Viruses and their multisystem impact: testing, tracking and therapy

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Agenda

- Herpes viruses, enteroviruses, and other species
- Associations of viruses with different health conditions:
  - Syndromes (ME/Fibromyalgia, etc.)
  - Autoimmune pathologies
  - Neurological conditions
  - Cancers
- SARS-CoV-2/COVID-19 and viral reactivation
- Testing techniques
- Checklists and other resources
- Therapies

We will focus on four different viral groupings

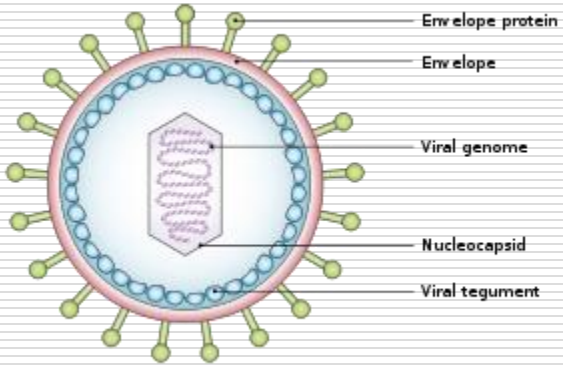
- Herpes viruses: Double-stranded DNA viruses
- Enteroviruses: Single-stranded RNA viruses
- Parvoviridiae: Single-stranded DNA genome
- Coronavirus SARS-CoV-2: Enveloped single-stranded RNA virus

Herpes viruses

The Herpes viruses are a large family of DNA viruses that cause infections and certain diseases in animals, including humans. Herpes viruses can cause both lytic and latent infections.

•8 key viruses in this family, all of which can be tested for:

1. Herpes simplex virus type 1 (HSV1, cold sores on lips, also fingers and hands)
2. Herpes simplex virus type 2 (HSV2, genital sores)
3. Varicella Zoster virus (also called herpes varicella/herpes zoster/shingles)
4. Epstein Barr virus (EBV)
5. Cytomegalovirus (CMV)
6. Human herpes virus 6 (HHV6)
7. Human herpes virus 7 (HHV7)
8. Human herpes virus 8 (HHV8, sometimes also called KSHV)



Simplified diagram of the structure of EBV

Source: https://en.wikipedia.org/wiki/Herpesviridae

Herpes Virus 1 & 2:
Herpes Simplex Virus 1 / 2 (HSV 1 / 2)

Virus: Herpes Simplex Virus (Human Herpes Virus HHV 1 / 2) (obligate intracellular), double-stranded DNA virus

Transmission: Saliva, sharing drinks, sexually transmitted

Symptoms (incubation time 2-20 days): Watery blisters on the skin or mucous membranes of the mouth, lips, genitals, anus, flu-like symptoms (fever, muscle aches, swollen lymph nodes, problems urinating, herpes keratitis (pain, light sensitivity, discharge))

Complications: Multiple Sclerosis (neurovirulent), loss of vision, encephalitis, latent infection; reactivation by organ transplantation or HIV: encephalitis, pneumonitis, bone marrow suppression

Herpes Virus 3:
Varicella Zoster Virus (VZV)

Virus: Varicella Zoster Virus (Human Herpes Virus HHV 3) (obligate intracellular organism), double-stranded DNA virus

Transmission: airborne, touching shingles blisters

Symptoms (incubation time 10-21 days): "Chickenpox" in younger people, "Herpes Zoster" in adults: Watery blisters on the skin, fever, tiredness, loss of appetite, headache

Complications: Encephalitis, pneumonia, bronchitis, 10-20% reactivation from nerve ganglia (Herpes Zoster), post-herpatic neuralgia, Mollaret´s meningitis, Zoster multiplex, "Ramsay Hunt syndrome" (painful blisters on tongue/ear, facial weakness, hearing loss), inflammation of arteries *(new study Journal of the American College of Cardiology, Vol. 70, Issue 2, July 2017, "Herpes Zoster increases risk of stroke and myocardial infarction" 23,233 patients had a higher risk of apoplectic stroke (35%) and myocardial infarction (59%) after Herpes Zoster)*

Herpes Virus 4:
Epstein Barr Virus (EBV)

Virus: Epstein Barr Virus (obligate intracellular), double stranded DNA virus, "Mononucleosis"

Transmission: "kissing disease", saliva, drinking from the same glass, toothbrush, blood, sex, blood-transfusion, organ transplantation

Symptoms (incubation period several weeks): fatique, fever, flu-like symptoms, nausea, loss of appetite, lymphadenitis (swollen lymph nodes in the neck), rash, sore throat, weakness, sore muscles

Complications: enlarged spleen, swollen liver, association with Non-Hodgkin Lymphoma

Very neurotropic – is attracted to the Central Nervous System

Herpes Virus 5:
Cytomegalovirus (CMV)

Virus: Cytomegalovirus (obligate intracellular), double-stranded DNA virus

Transmission: body fluids (urine, saliva, breast milk, sexual transmission), organ transplantation, blood transfusion

Symptoms (incubation period several weeks): fatique, fever, flu-like symptoms, lymphadenitis (swollen cervical lymph nodes), sore throat, splenomegaly

Complications: congenital infection with hearing loss, vision loss, seizures, mental disabilities, lack of coordination; immune suppressed patients: hepatitis, colitis, retinitis, pneumonitis, esophagitis, polyradiculopathy, transverse myelitis, subacute encephalitis; arterial hypertension, artheroscleroris, aortic aneurysms; association with Non-Hodgkin Lymphoma

Also very neurotropic –attracted to the CNS

Herpes Virus 6:
Human Herpes Virus 6 (HHV6), roseola/exanthem subitum

Virus: Human Herpes Virus 6 (obligate intracellular), double-stranded DNA virus, one of the Herpes viruses

Transmission: Saliva, latency in salivary glands, haematopoetic (blood-building) system

Symptoms: Exanthema subitum (roseola infantum, sixth disease) with high temperature followed by a rash;

Complications: Multiple Sclerosis (neurovirulent), cofactor in M.E./CFS, fibromyalgia, AIDS, optic neuritis, cancer, temporal lobe epilepsy, Hashimoto thyroiditis, liver dysfunction, liver failure; reactivation by organ transplantation: encephalitis, pneumonitis, bone marrow suppression

Herpes Virus 7:
Human Herpes Virus 7 (HHV-7)

Virus: HHV-7 belongs to the group of β-herpesviridae (obligate intracellular), double-stranded DNA virus

Transmission: Birth canal, breast milk, saliva and allogeneic blood product or transplants.

Symptoms: HHV-7 infections may be asymptomatic or associated with fever or febrile seizures. May occur with or without rash (Exantema subitum), vomiting, diarrhea, low lymphocyte counts

Complications: Neurological complications that occur alongside febrile diseases, e.g. infectious seizures and temporary hemiplegia, febrile epilepticus or clinical and laboratory signs of meningitis; seizures occur more frequently in reactivated infections

Source: Yoshikawa T, Ihira M, Suzuki K, Matsubara T, Furukawa S, Asano Y, Invasion by human herpesvirus 6 and human herpesvirus 7 of the central nervous system in patients with neurological signs and symptoms, Arch Dis Child 2000 Aug; 83(2): 170-1

Herpes Virus 8:
Human Herpes Virus 8 (HHV-8; Kaposi's sarcoma herpes virus KSHV)

Virus: HHV-8 belongs to the group of herpesviridae, double-stranded DNA virus, one of the Herpes viruses

Transmission: Respiratory droplets and nasal secretions, shedding of viral particles into saliva, sexual transmission, intravenous drug use. Prevalences of between 30 and 80 % in Sub-Saharan Africa

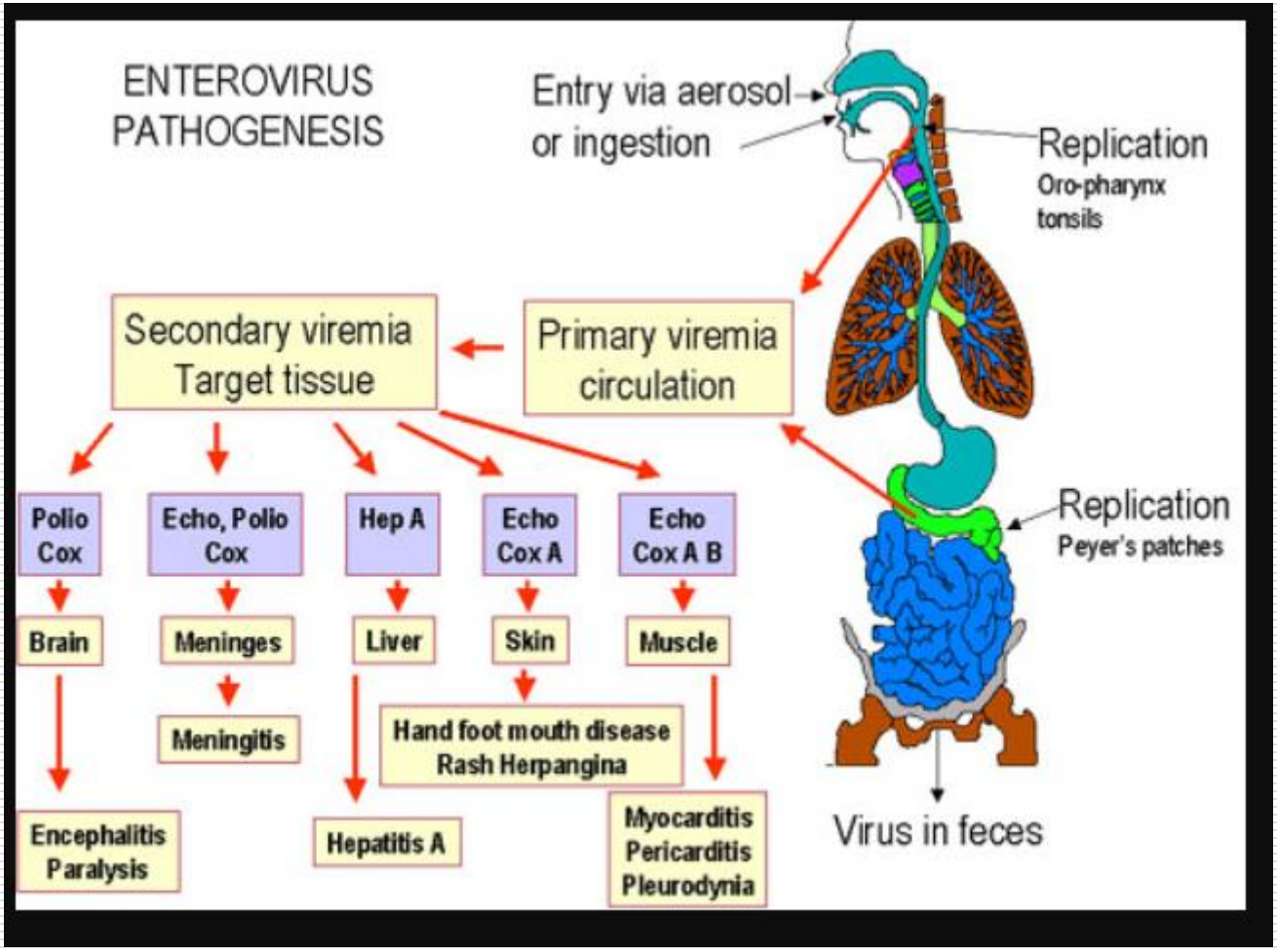
Symptoms: Fever, maculopapular rash, lymphadenopathy, enlarged spleen

Complications: A blood disorder known as pancytopenia, bone marrow failure, rapid progression to Kaposi´s sarcoma

Risk factors: Immune suppression, cancer

Source: Yoshikawa T, Ihira M, Suzuki K, Matsubara T, Furukawa S, Asano Y, Invasion by human herpesvirus 6 and human herpesvirus 7 of the central nervous system in patients with neurological signs and symptoms, Arch Dis Child 2000 Aug; 83(2): 170-1

Pathogenesis of enteroviruses



Source: http://www.microbiologybook.org/virol/picorna.htm

Diseases caused by enteroviruses

PATHOLOGY

Table 4 Human diseases caused by enteroviruses

	Poliovirus	Coxsackie A virus	Coxsackie B virus	Echovirus	Enterovirus (other)
Asymptomatic infection	yes	yes	yes	yes	yes
Meningitis	yes	yes	yes	yes	yes
Paralysis	yes	yes	yes	yes	?*
Febrile exanthems	no	yes	yes	yes	yes
Acute respiratory disease	no	yes	yes	yes	yes
Myocarditis	no	yes	yes	yes	no
Orchitis	no	no	yes	yes	no

* Enterovirus-D68 (EV-D68) can replicate in blood and may damage the central nervous system. It has been detected in cerebrospinal fluid of patients with acute flaccid paralysis.

There have been reports of children hospitalized with muscle weakness or paralysis, usually in their arms and legs. They were tested for poliovirus, West Nile virus, and enteroviruses. About half of the children had EV-D68 in their nose secretions; usually, EV-D68 affects the respiratory system and it is not yet known if this respiratory infection is linked to their muscle weakness.

Source: http://www.microbiologybook.org/virol/picorna.htm

Enterovirus:
Coxsackie Virus A & B

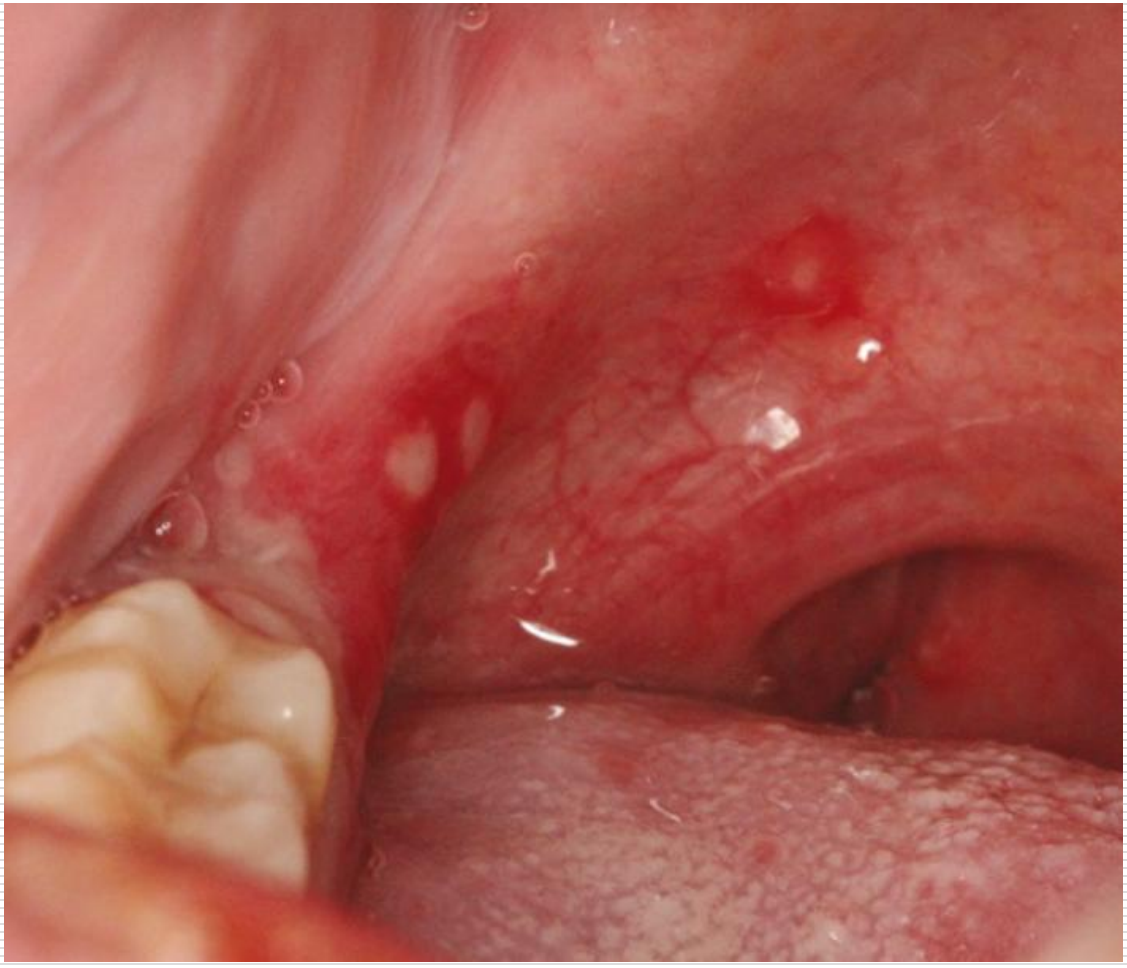
Virus: Coxsackie Virus (obligate intracellular), belongs to the Picornaviridae/enterovirus family (also includes Polio); it is a single-stranded RNA virus divided into group A and group B

Transmission: Contagious, can easily spread from person to person: faecal-oral contamination, droplets of fluid from sneezes/coughs, body fluids, utensils, toys, diaper-changing table

Symptoms: Gastrointestinal (from "entero"), intestinal permeability Group A: Herpangina, AHC (acute hemorrhagic conjunctivitis, HFM (hand-foot-and-mouth disease); Group B: Myocarditis, pericarditis, pleurodynia, hepatitis; Group A and B: fever, rashes, sore throat, diarrhoea, cough, fatigue, conjunctivitis, loss of appetite, headache, night sweats, aseptic meningitis

Complications: CNS disease similar to poliomyelitis, systemic neonatal disease, insulin-dependent diabetes mellitus, Group A: generalized myositis with flaccid paralysis, Group B: focal muscle injury, degeneration of neuronal tissue with spastic paralysis

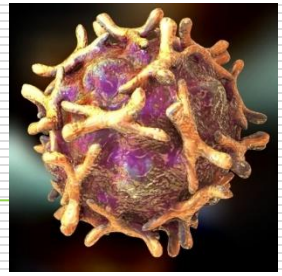
Enterovirus:
Coxsackie may cause Herpangina



Can cause Herpangina: small and symmetrical ulcers of herpangina on the soft palate and retromolar pad, also sometimes simply called ulcers, or aphthous ulcers

Source: ***https://www.uptodate.com/contents/image?imageKey=PEDS%2F127342***

Enterovirus: Echovirus



Virus: Echovirus ("Enteric cytopathic human orphan virus"), belongs to the Picornaviridae family; single-stranded RNA virus

Transmission: Contagious, can easily spread from person to person: faecal-oral contamination, respiratory droplets, body fluids, nosocomial route

Symptoms: Gastrointestinal (from "entero"), intestinal permeability; depend on the site of infection: may involve breathing difficulties, harsh cough, mouth sores, sore throat, fever and chills, chest pain, severe headaches, photosensitivity, nausea and vomiting, eruptive skin rash

Complications: Commonly associated with M.E./CFS: ""Finding enterovirus [viral capsid protein 1] protein in 82% of stomach biopsy samples seems to correlate with the high percentage of CFS patients with GI complaints"[1], if the infection affects the membranes covering the brain and spinal cord: meningitis, paralysis; chest pain if the infection affects the heart muscle or sac-like covering around the heart (pericarditis); acute flaccid paralysis/acute transverse myelitis, mental status changes

Source: https://free3d.com/3d-model/echovirus-3050.html; https://medlineplus.gov/ency/article/001340.htm#:~:text=Mouth%20sores-,Skin%20rashes,brain%20and%20spinal%20cord%20(meningitis); 1. Chia, Jean-San & Chia, A.Y.. (2008). Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach. Journal of clinical pathology. 61. 43-8.

Parvoviridiae:
Parvovirus B19

Virus: A very small non-enveloped DNA virus

Transmission: common and highly contagious, spreads through respiratory secretions, such as saliva, sputum, or nasal mucus, when an infected person coughs or sneezes. Parvovirus B19 can also spread through blood or blood products.

Symptoms: Sometimes called slapped-cheek disease because of the distinctive face rash that develops; lethargy; loss of appetite; abdominal pain and bloating; fever or low body temperature (hypothermia); vomiting; and severe, often bloody, diarrhea.

Complications: Can lead to serious health problems for the foetus (incl. miscarriage, stillbirth) in pregnant women. Painful or swollen joints (polyarthropathy syndrome), severe anaemia; persistent vomiting and diarrhea can cause rapid dehydration, and damage to the intestines and immune system can cause septic shock.

Source: https://www.cdc.gov/parvovirusb19/about-parvovirus.html

Agenda

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- **Associations of viruses with different health conditions**
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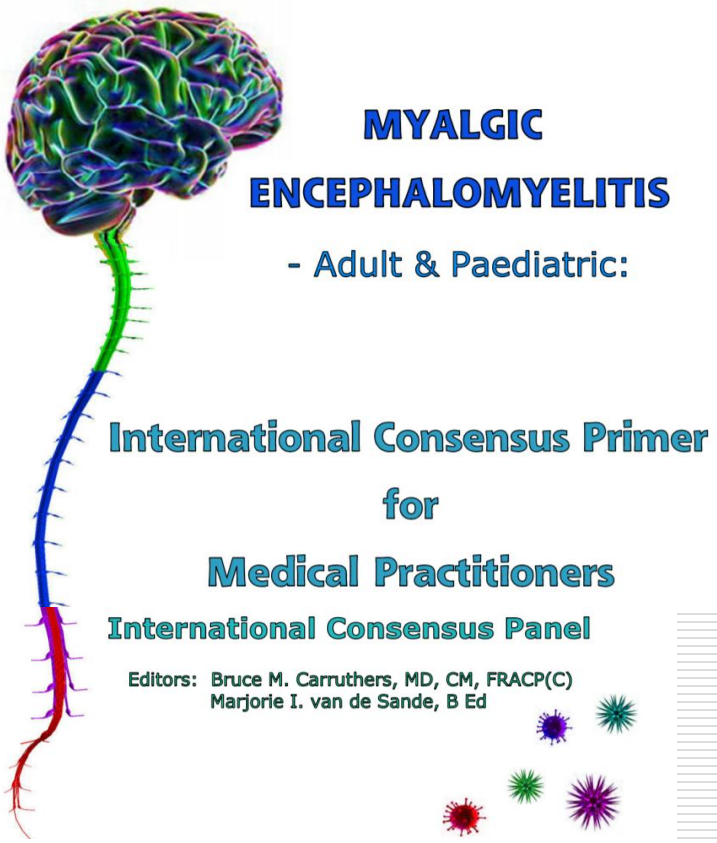
The ME International Consensus Primer recommends considering EBV, CMV, HHV-6 and enteroviruses

M.E.



& DIAGNOSTIC WORKSHEET

□ flares with exertion; □ crimson crescents in the tonsillar fossa: □ demarcated along margins of both anterior and pharyngeal pillars, □ if patient has no tonsils, they assume a posterior position in the oropharynx; □ splenomegaly

GI: □ increased bowel sounds, □ abdominal bloating, □ abdominal tenderness: epigastrium (stomach), right lower quadrant (terminal ileum) and left lower quadrant (sigmoid colon) – *most patients have tenderness in 2-3/3 areas*

Cardiovascular & respiratory: □ arrhythmias: □ BP as above; □ mottling of extremities, □ extreme pallor, □ Raynaud's phenomenon, □ receded moons of finger nails (chronic phase) _____

Laboratory/Investigative Protocol: Diagnose by criteria. Confirm by laboratory and other investigations. A broad panel of tests provides a more robust basis to identify symptom patterns, abnormalities and orient treatment.

Routine laboratory investigation: □ CBC, □ ESR, □ CA, □ P, □ RBC Mg, □ vitamin D3, □ B12 & folate, □ ferritin, □ zinc, □ FBS, □ PC, □ Hb A1C, □ serum electrolytes, □ TSH, □ protein electrophoresis screen, □ CRP, □ creatinine, □ ECG (U+ T wave notching), □ CPK and liver function, □ rheumatoid factor, □ antinuclear antibodies, □ urinalysis, □ essential fatty acids, □ CoEnzyme Q10, □ immunoglobulins, □ diurnal cortisol levels, □ TTG, □ serotonin

Additional laboratory investigation: *(as indicated by symptoms, history, clinical evaluation, lab findings, risk factors)* □ 24 hour urine free cortisol, □ DHEA sulphate, □ ACTH, □ chest x-ray, □ hormones including free testosterone □ panoramic x-ray of dental roots, □ amino acid profile, □ abdominal ultra sound, □ lactose/fructose breath test

Further testing with specificity to ME, *if and as indicated*. *Some tests are in the research stage but can identify abnormalities and focus treatment. Viral tests should be interpreted by a physician experienced in these infections.*

Pathogen	*Tests*	*Pathogen*	*Tests*
□ Enterovirus	RT-PCR, serology, stomach biopsy	□ mycoplasma	DNA-PCR, serology
□ EBV, □ CMV, □ HHV-6	DNA-PCR, serology, antigenemia	□ Borrelia burgdorferi	DNA-PCR, serology, Western Blot
□ Clamydia pneumonia	DNA PCR, serology	□ Parvovirus B19	DNA-PCR, IgG, IgM,

Immune system profiles: □ ***↓NK cell function & ↑ cytotoxicity**; □ B & T-cell function: □ IgG, □ IgG subclasses 1-4; □ IgA, □ IgM (shift from T1 to T2), □ cytokine/chemokine profile panel (94% accuracy): IL-8, IL-13, MIP-1β, MCP-1, IL4, □ flow cytometry for ↑ lymphocyte activity, □ ↑ 37 kDa 2-5A RNase L immunoassay – defect/ratio & bioactivity, □ food sensitivity panel, □ chemical sensitivities, □ stool for WCB - D-lactic acid bacteria balance, ova & parasites, □ autoimmune profile, **Intestinal dysbiosis:** □ IgA & IgM for intestinal aerobic bacteria in serum, □↑ leukocyte elastase activity in PBMCs, □ IgG food intolerance test, □ toxoplasmosis

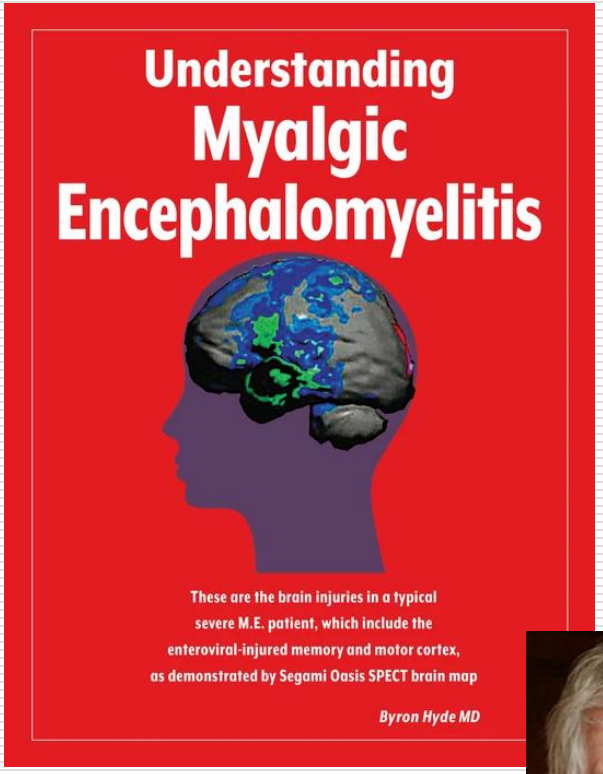
Neurological & static testing: □ ***SPECT scan with contrast - ↓** cortical/cerebellar region cerebral blood flow (rCBF) in the frontal, parietal, temporal and occipital & brain stem regions - *more brain involvement indicates increased illness severity*, □ **MRI of brain –** *(increased T2-weighted images in high white matter tracts & loss of GM volume) & rule out MS*, □ **MRI of spine** *(dynamic disc bulges/herniation , stenosis)*, □ **sleep study** *(↓ stage 4 sleep, sleep pattern & rule out treatable sleep dysfunctions – upper airway resistance syndrome, sleep apnea, etc.)*

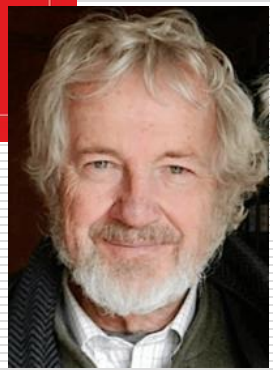
PENE: *A 2 consecutive day comprehensive 8-12 minute cardiopulmonary exercise stress test (measuring heart, lung, and metabolic function) - only ME patients have significantly worse scores the second day & abnormal recovery from exertion.*

* **Exercise tolerance test with expired gas exchange** - (2 consecutive days) – *measure cardiovascular, pulmonary &*

Source: https://doctorswith.me/international-consensus-primer-for-medical-practitioners/

Dr. Byron Hyde sees Enteroviruses as the key driver of M.E.





Item 2:
The Basic Characteristics of M.E.

M.E. is the chronic stage of an encephalitic enteroviral infection of the central nervous system (CNS) similar, but less lethal than, that caused by polio enteroviruses 1, 2 and 3.

1. Myalgic Encephalomyelitis is a chronic, **and only**, enteroviral caused disease. The M.E. encephalitic features are less initially apparent, than in polio.
2. An incubation period of two to six days occurs before the first symptoms of illness appear.
3. In adults, as with polio, the illness may begin with the appearance of biphasic symptoms. The first phase may be missed in sporadic cases. In both illnesses the initial biphasic symptoms may be "cold like" or gastric but often these are so slight they may be missed.
4. The second phase of M.E. illness is the encephalitic, meningitic-like associated with muscular symptom phase followed weeks or months later by the cascading features (discussed later).
5. In northern latitudes M.E. occurs primarily from June to early November, peaking in late summer.
6. HMPAO brain SPECT scan demonstrates a permanent micro-vascular injury to the CNS from the first few days of acute illness.
7. Brain injury as seen on SPECT brain scans clearly with Segami Oasis software. **Injury in M.E. always involves the anterior left temporal lobe and left posterior cingulate gyrus** and frequently the left motor cortex. These hypo-perfusion CNS injuries are consistent with, and explains, the memory and muscle disfunction in M.E. patients.

Videos and PPTs on the topic by Dr. Byron Hyde:
https://aonm.org/2019-improving-patients-lives/

Source: https://www.nightingale.ca/_files/ugd/5b307e_b3a662c05f174937b9516d473a994c41.pdf

Fibromyalgia and Epstein Barr Virus/CMV

Fibromyalgia

Journal of Neurology and Neuroscience

Evaluation of Antiviral Antibodies against Epstein-Barr Virus and Neurotransmitters in Patients with Fibromyalgia

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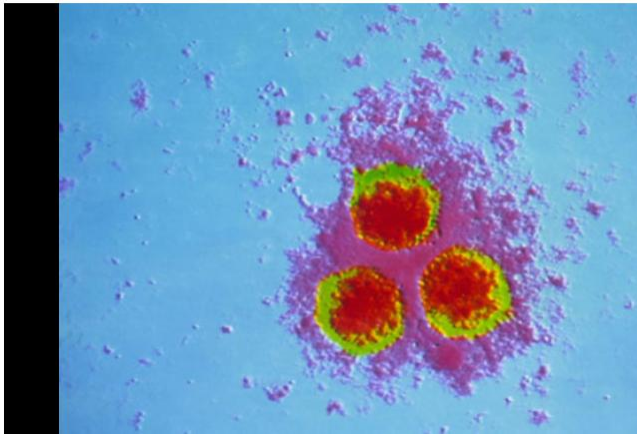
Abstract

Fibromyalgia (FM) is characterized by chronic widespread pain lasting for a minimum of three months, and pain at mechanical pressure in at least 11 of the 18 tender points. The cause of fibromyalgia is unknown. Several hypotheses have been developed including "central sensitization". This theory proposes that fibromyalgia patients have a lower threshold for pain because of increased reactivity of painsensitive neurons in the spinal cord or brain. Some researchers supposed that different

"The obtained results revealed that high EBV IgG concentrations in the serum of patients with FM correlated with pain intensity and associated clinical symptoms. This is consistent with the fact that FM is connected to the immune response to certain infectious agents (e.g. EBV, CMV)."

Fibromyalgia and Varicella Zoster Virus (VZV)

Varicella-zoster virus



Varicella Zoster Virus (VZV) - a highly contagious virus that spreads from person-to-person by coughing or sneezing, or through direct contact with the characteristic skin lesions it causes or fluids from blisters on an infected person.

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doi: 10.1007/82_2009_3

Neurological Disease Produced by Varicella Zoster Virus Reactivation Without Rash

Don Gilden, Randall J. Cohrs, Ravi Mahalingam, and Maria A. Nagel

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Abstract

Go to:

Reactivation of varicella zoster virus (VZV) from latently infected human ganglia usually produces herpes zoster (shingles), characterized by dermatomal distribution pain and rash. Zoster is often followed by chronic pain (postherpetic neuralgia or PHN) as well as meningitis or meningoencephalitis, cerebellitts, isolated cranial nerve palsies that produce ophthalmoplegia or the Ramsay Hunt syndrome, multiple cranial nerve palsies (polyneuritis cranialis), vasculopathy. myelopathy, and various inflammatory disorders of the eye. Importantly, VZV reactivation can produce chronic radicular pain without rash (zoster sine herpete), as well as all the neurological disorders listed above without rash. The protean neurological and ocular disorders produced by VZV in the absence of rash are a challenge to the practicing clinician. The

"Zoster is often followed by chronic pain (postherpetic neuralgia)"

Source: https://www.clinicaladvisor.com/varicella-zoster-virus/slideshow/377/

M.E. | Fibromyalgia

Association of Parovirus B19 with ME/CFS as well as fibromyalgia

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DOI: 10.2478/prolas-2019-0065

ASSOCIATION OF HUMAN PARVOVIRUS B19 INFECTION WITH DEVELOPMENT AND CLINICAL COURSE OF MYALGIC ENCEPHALOMYELITIS / CHRONIC FATIGUE SYNDROME

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Contributed by Modra Murovska

Our aim was to estimate the presence of B19V infection markers, the level of cytokines and time period since the appearance of infection in association with ME/CFS clinical symptoms. In 200 ME/CFS patients and 104 control group individuals the presence of B19V-specific IgG/IgM class antibodies, B19V NS1 gene sequence, mRNA expression, viral load and level of cytokines were determined. B19V-specific IgG-antibodies were found in 70% of ME/CFS patients and 67.4% of controls, IgM-antibodies in 8% of patients and in none of controls, B19V genomic sequences in 29% of patients and 3.8% of controls. 58.6% of positive patients had active and 41.4% had latent/persistent B19V infection. B19V NS1 gene expression was detected in 43% of patients. B19V load varied from < 0.2 copies to median 38.2 copies/μg of DNA. According to the antibody pattern, 36% of patients had a recent, and 43% had sustained B19V infection. Patients with the B19V genomic sequence and NS1 specific antibodies significantly more often had lymphadenopathy and multi-joint pain. Onset of the symptoms corresponded to time of appearance of B19V infection. IL-10 and TNF- levels were higher in patients with elevated B19V load. B19V genome 1 was identified in Latvian ME/CFS patients. The results indicated that at least in some cases

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Human Parvovirus B19 Infection Status in Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Fibromyalgia

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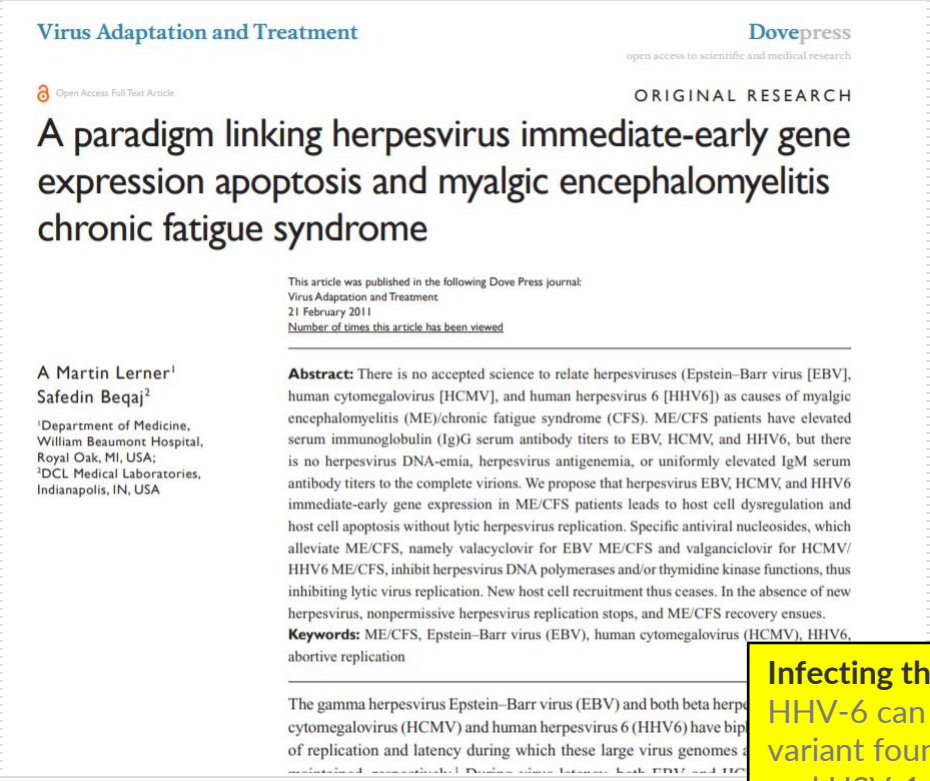
Abstract

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and fibromyalgia (FM) are chronic diseases with unclear aetiology. Human parvovirus B19 (B19) is immunomodulatory single-stranded DNA virus, which belongs to *Parvoviridae* family, *Parvovirinae* subfamily and *Erythrovirus* genus. B19 is considered as a possible pathogen or trigger factor in development of ME/CFS and FM.

Source: https://www.sciendo.com/article/10.2478/prolas-2019-0065;
https://www.rsu.lv/en/scientific-papers/human-parvovirus-b19-infection-status-patients-myalgic-encephalomyelitischronic

Herpes viruses are often involved in neurological disease



Virus Adaptation and Treatment

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ORIGINAL RESEARCH

A paradigm linking herpesvirus immediate-early gene expression apoptosis and myalgic encephalomyelitis chronic fatigue syndrome

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Virus Adaptation and Treatment
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A Martin Lerner[1]
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Abstract: There is no accepted science to relate herpesviruses (Epstein–Barr virus [EBV], human cytomegalovirus [HCMV], and human herpesvirus 6 [HHV6]) as causes of myalgic encephalomyelitis (ME)/chronic fatigue syndrome (CFS). ME/CFS patients have elevated serum immunoglobulin (Ig)G serum antibody titers to EBV, HCMV, and HHV6, but there is no herpesvirus DNA-emia, herpesvirus antigenemia, or uniformly elevated IgM serum antibody titers to the complete virions. We propose that herpesvirus EBV, HCMV, and HHV6 immediate-early gene expression in ME/CFS patients leads to host cell dysregulation and host cell apoptosis without lytic herpesvirus replication. Specific antiviral nucleosides, which alleviate ME/CFS, namely valacyclovir for EBV ME/CFS and valganciclovir for HCMV/ HHV6 ME/CFS, inhibit herpesvirus DNA polymerases and/or thymidine kinase functions, thus inhibiting lytic virus replication. New host cell recruitment thus ceases. In the absence of new herpesvirus, nonpermissive herpesvirus replication stops, and ME/CFS recovery ensues.

Keywords: ME/CFS, Epstein–Barr virus (EBV), human cytomegalovirus (HCMV), HHV6, abortive replication

The gamma herpesvirus Epstein–Barr virus (EBV) and both beta herpe
cytomegalovirus (HCMV) and human herpesvirus 6 (HHV6) have bip
of replication and latency during which these large virus genomes a

"We propose that herpesvirus EBV, HCMV, and HHV6 immediate-early gene expression in ME/CFS patients leads to host cell dysregulation and host cell apoptosis without lytic herpesvirus replication. Specific antiviral nucleosides, which alleviate ME/CFS, namely valacyclovir for EBV ME/CFS and valganciclovir for HCMV/ HHV6 ME/CFS, inhibit herpesvirus DNA polymerases and/or thymidine kinase functions, thus inhibiting lytic virus replication. New host cell recruitment thus ceases. In the absence of new herpesvirus, nonpermissive herpesvirus replication stops, and ME/CFS recovery ensues."

Infecting the brain via the Olfactory Nerve, Limbic Encephalitis

HHV-6 can travel to the brain through the nose, and is also the dominant variant found in the sensory ganglia (Hufner 2007). Like HHV-6, measles and HSV-1 tend to affect the limbic system as well as the hippocampus (Harberts 2011). There have been a number of abnormalities found in CFS patients in the hippocampus: reduced concentration of N-acetylaspartate, (Brooks 2000), hippocampal atrophy and 5-HT1A receptor binding in the hippocampus (Cleare 2005).[1]

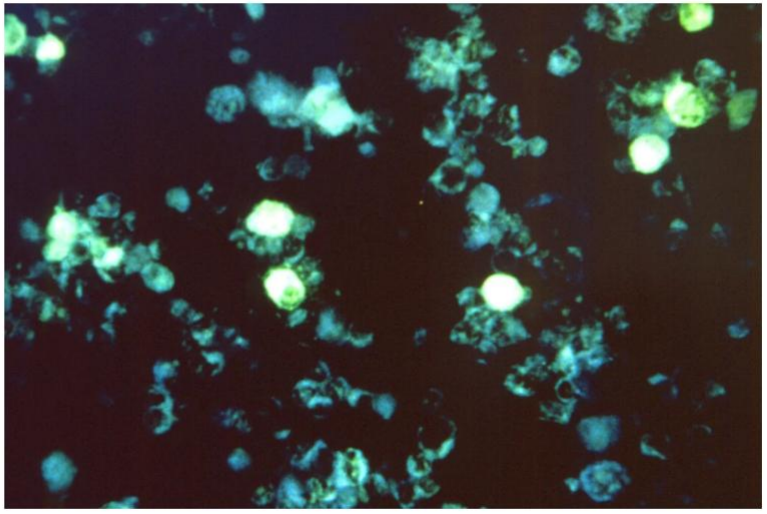
Source: 1. https://hhv-6foundation.org/associated-conditions/hhv-6-and-chronic-fatigue-syndrome

Published on 13th January 2022 in "Science": EBV

The Harvard Gazette

HEALTH & MEDICINE

Epstein-Barr virus may be leading cause of MS



Cells infected with Epstein-Barr, a common herpes virus that can cause mononucleosis and establishes a latent, lifelong infection of the host.

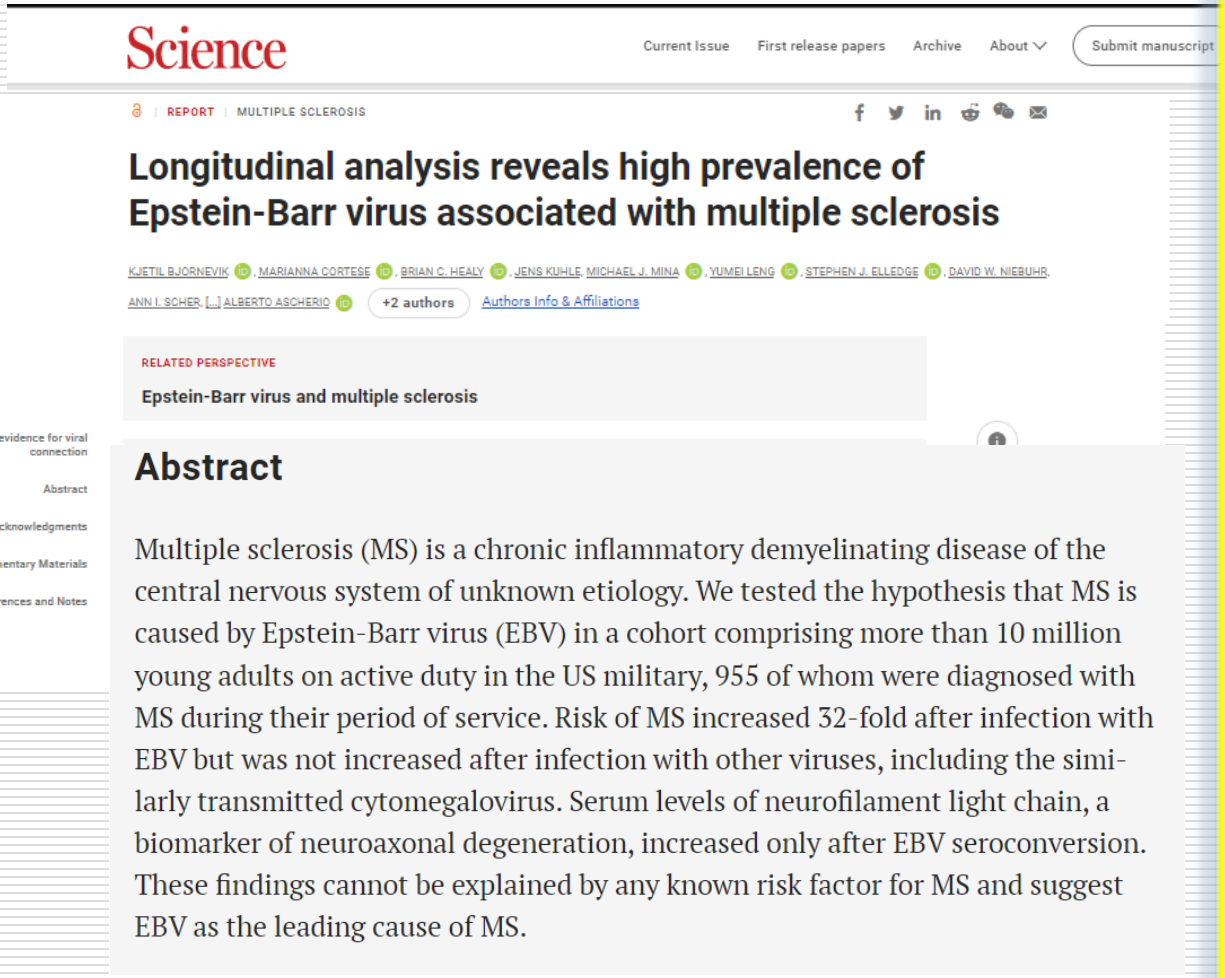
CDC

First study to provide 'compelling evidence of causality'

"The hypothesis that EBV causes MS has been investigated by our group and others for several years, but this is the first study providing compelling evidence of causality," said Alberto Ascherio, professor of epidemiology and nutrition at Harvard Chan School and senior author of the study. "This is a big step because it suggests that most MS cases could be prevented by stopping EBV infection, and that targeting EBV could lead to the discovery of a cure for MS."

Source: *https://news.harvard.edu/gazette/story/2022/01/epstein-barr-virus-may-be-leading-cause-of-multiple-sclerosis/*

The study found that the risk of developing MS increased 32-fold following EBV infection



Science

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REPORT | MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

KJETIL BJORNEVIK, MARIANNA CORTESE, BRIAN C. HEALY, JENS KUHLE, MICHAEL J. MINA, YUMEI LENG, STEPHEN J. ELLEDGE, DAVID W. NIEBUHR, ANN I. SCHER, [...] ALBERTO ASCHERIO +2 authors Authors Info & Affiliations

RELATED PERSPECTIVE

Epstein-Barr virus and multiple sclerosis

Stronger evidence for viral connection

Abstract

Acknowledgments

Supplementary Materials

References and Notes

Abstract

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

"Using data from more than ten million United States military recruits monitored over a 20-year period, 955 of whom were diagnosed with MS during their service, Kjetil Bjornevik *et al.* tested the hypothesis that MS is caused by EBV. They found that the risk of developing MS in individuals who were EBV-negative increased by 32-fold following EBV infection. "These findings," say the authors, "cannot be explained by any known risk factor and suggest EBV as the leading cause of MS."

Source: https://www.science.org/doi/10.1126/science.abj8222; https://www.eurekalert.org/news-releases/939665

Journal of Alzheimer's Disease: HSV1/herpes encephalitis specifically identified

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Published in final edited form as:
J Alzheimers Dis. 2016; 51(4): 979–984.
doi: 10.3233/JAD-160152
PMCID: P
NIHMSID: NI

Microbes and Alzheimer's Disease

Ruth F. Itzhaki,[a,*] Richard Lathe,[b,*] Brian J. Balin,[c] Melvyn J. Ball,[d] Elaine L. Bearer,[e] Heiko Braak,[f] Maria J. Chris Carter,[h] Mario Clerici,[i] S. Louise Cosby,[j] Kelly Del Tredici,[f] Hugh Field,[k] Tamas Fulop,[l] Claudio Grassi, Griffin,[n] Jürgen Haas,[b] Alan P. Hudson,[o] Angela R. Kamer,[p] Douglas B. Kell,[q] Federico Licastro,[r] Luc Letenr Lövheim,[t] Roberta Mancuso,[u] Judith Miklossy,[v] Carola Otth,[w] Anna Teresa Palamara,[x] George Perry,[y] Chris Preston,[z] Etheresia Pretorius,[aa] Timo Strandberg,[bb] Naji Tabet,[cc] Simon D. Taylor-Robinson,[dd] and Judith A. Hudson[ee]

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We are researchers and clinicians working on Alzheimer's disease (AD) or related topics, and we write express our concern that one particular aspect of the disease has been neglected, even though treatment based on it might slow or arrest AD progression. We refer to the many studies, mainly on humans, implicating specific microbes in the elderly brain, notably herpes simplex virus type 1 (HSV1), *Chlam pneumoniae*, and several types of spirochaete, in the etiology of AD [1–4]. Fungal infection of AD bra 6] has also been described, as well as abnormal microbiota in AD patient blood [7]. The first observati of HSV1 in AD brain were reported almost three decades ago [8]. The ever-increasing number of these studies (now about 100 on HSV1 alone) warrants re-evaluation of the infection and AD concept.

AD is associated with neuronal loss and progressive synaptic dysfunction, accompanied by the deposition

"There is incontrovertible evidence that Alzheimer's Disease has a dormant microbial component. We can't keep ignoring all of the evidence"

Professor Douglas Kell, Manchester University

"We refer to the many studies, mainly on humans, implicating specific microbes in the elderly brain, **notably herpes simplex virus type 1 (HSV1),** *Chlamydia pneumoniae*, and several types of spirochaete, in the etiology of AD [1–4]."

Viral involvement in autoimmunity is well documented ...

- Viruses: molecular mimicry, bystander activation or viral persistence? – possibly a perfect storm of all three
- Examples:
  - SLE (Lupus)
  - Type 1 Diabetes
  - Ulcerative colitis
  - Sarcoidosis
  - Myasthenia Gravis
  - Graves' Disease

… in autoimmune neuropsychiatric syndromes (PANS/PANDAS), too

Autoimmune neuropsychiatric disorders

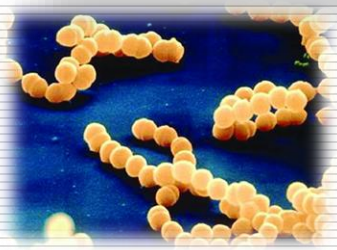
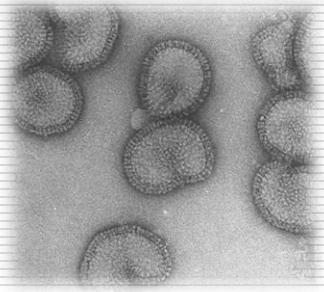
- **Group A streptococci**
- **Influenza A**
- **Varicella Zoster (VZV)**
- **Mycoplasma**
- **Lyme disease**
- **Babesia**
- **Bartonella**
- **Coxsackie virus**

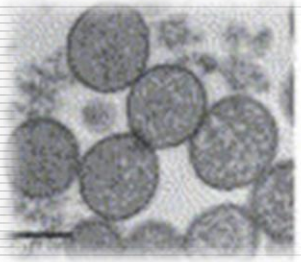
BIOLOGY | HEALTH

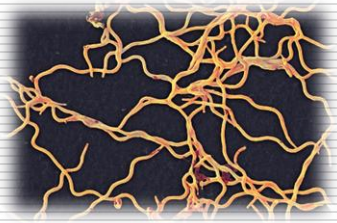
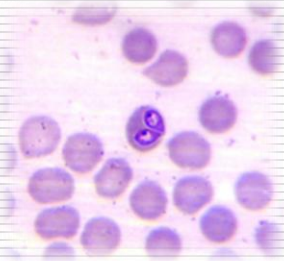
Yes, You Can Catch Insanity

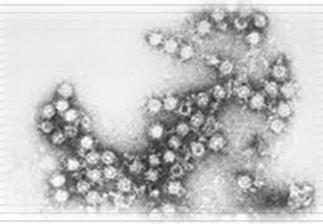
A controversial disease revives the debate about the immune system and mental illness.

BY ANDREW CURRY
ILLUSTRATION BY HADLEY HOOPER
APRIL 16, 2015



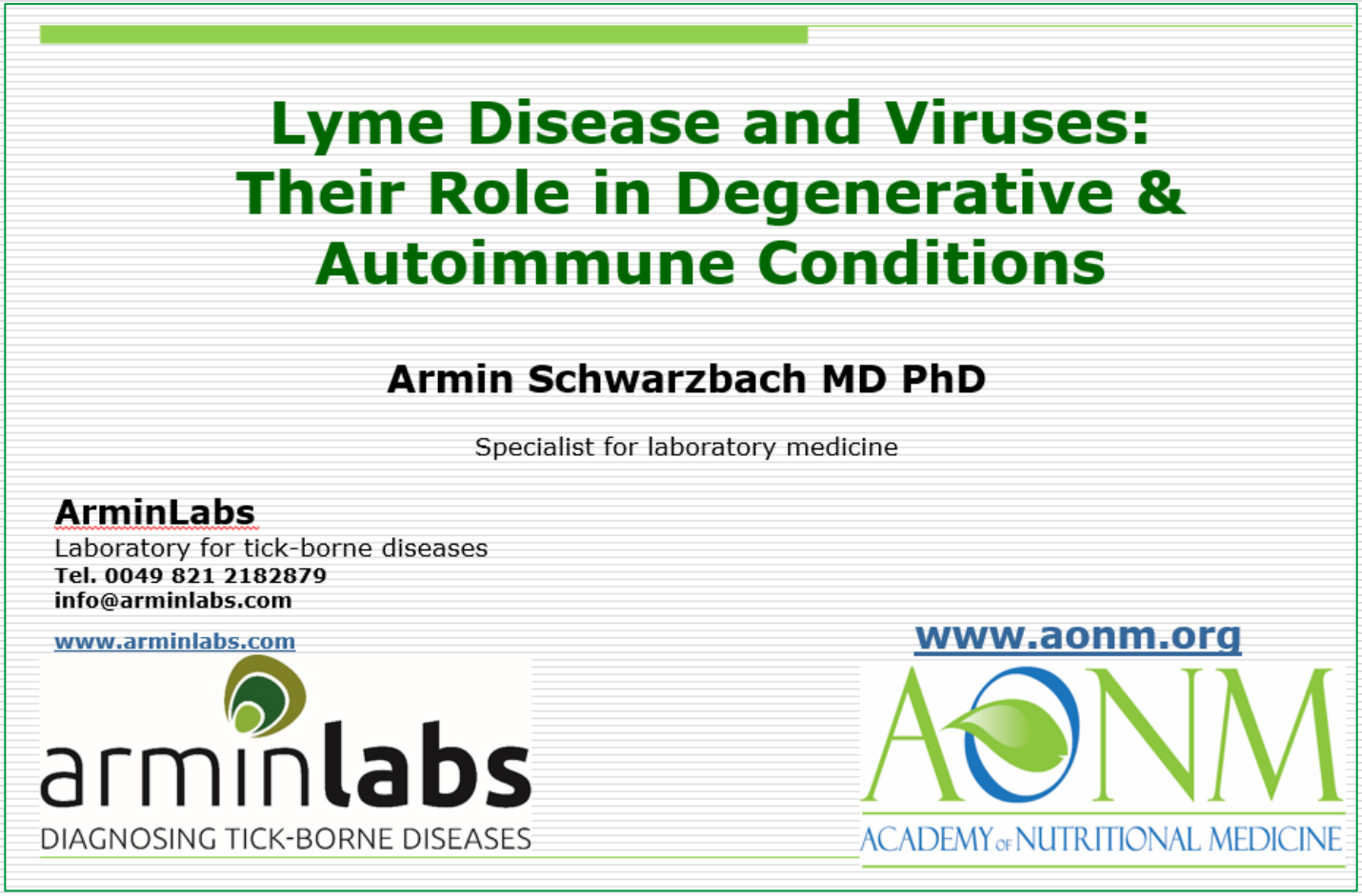


Patients often have more than one infection, and can be subclinical

See: https://aonm.org/cunningham-panel-panspandas/

Full presentation on viruses in autoimmunity on the AONM website

https://aonm.org/viruses-and-testing/



What cancers are viruses associated with?

- Myelodysplastic syndromes
- Leukaemia
- Lymphomas/Non-Hodgkin's Lymphoma

B-Cell Non-Hodgkin's Lymphoma: EBV/CMV

- Epstein Barr Virus-associated Non-Hodgkin's lymphoma of B-cell origin, Hodgkin's disease, acute leukemia, and systemic lupus erythematosus: a serologic and molecular analysis, Mitarnun W et al, http://www.ncbi.nlm.nih.gov/pubmed/12188384
- EBV-Associated Lymphoproliferative Disorders: Classification and Treatment, Carbone A et al, The oncologist 1083-7159/2008
- Cytomegalovirus infection in patients with lymphoma: an important cause of morbidity and mortality. Torres HA et al. Clin. Lymphoma Myeloma, 2006 Mar;6(5): 393-8

Source: http://www.clevelandclinicmeded.com/medicalpubs/diseasemanagement/pulmonary/sarcoidosis/

"How EBV causes blood cancer", study, University of Sussex - report November 2016

Scientists reveal how a common virus triggers blood cancer

Scientists at the University of Sussex, trying to uncover how the common Epstein-Barr virus causes blood cancer in adults and children, have discovered how the virus takes control of two genes involved in cancer development so it can switch them on or off.

Professor Michelle West

The research team, led by Professor Michelle West, set out to determine how the Epstein-Barr virus controls two genes; *MYC*, a gene known to drive cancer development when it is altered or switched on at high level and *BCL2L11*, a gene which normally triggers cell death to prevent cancer, but can be turned off by the virus.

With thanks to funding from the blood cancer charity Bloodwise, the scientists discovered that the virus controls the *MYC* and *BCL2L11* genes by hijacking 'enhancer' DNA regions which are situated far away from the genes. These enhancers act as 'control centres' and are able to contact and control genes from long distances by the looping out of the intervening stretches of DNA.

Professor West's team found that Epstein-Barr virus turns on the *MYC* gene by increasing contacts between a specific set of enhancers and the gene. The scientists believe this may explain how the virus causes the changes to the *MYC* gene that are found in Burkitt's lymphoma.

The team also discovered new enhancers which control the *BCL2L11* gene. In this case, they found that Epstein-Barr virus stops these control centres from contacting the gene. Encouragingly the team have discovered that this blocking effect can be reversed by using a specific drug - paving the way for new treatments.

Professor West said: "This is a key step towards uncovering how this common virus which, affects thousands of people every year, causes blood cancer.

"It is now important to carry out further studies to c tell us more about how the virus drives lymphoma developmen ugs."

Dr Alasdair Rankin, Research Director at Bloodwis , but we were never sure of the exact mechanisms. These behaviour of genes that control cancer growth.

Professor West said: "This is a key step towards uncovering how this common virus which, affects thousands of people every year, causes blood cancer."

"By mapping out the complex genetic interactions that help lymphoma cells grow and survive, this research can guide the design of new treatments to target the disease. It may also help to identify those drugs currently used to treat other diseases that could be effective in treating these types of lymphoma."

… as well as tailored testing panels (on request)

» Lymphoma/leukaemia/myeloma:

1. Borrelia ELISpot
2. Babesia ELISpot
3. Ehrlichia/Anaplasma ELISpot
4. Coxiella IgG/IgM antibodies
5. EBV ELISpot
6. CMV ELISpot
7. VZV ELISpot
8. CD3/ CD56/ CD57 cells

Monoclonal gammopathy:

1. Bartonella ELISpot
2. CD3/ CD56/ CD57 cells

Glioblastoma/brain cancer:

1. Borrelia-ELISpot
2. Mycolasma pneumoniae ELISpot + IgG/IgA antibodies
3. Toxoplasma IgG/IgM antibodies
4. CD3/ CD56/ CD57 cells

Prostate cancer:

1. Chlamydia pneumoniae ELISpot + IgG/IgA antibodies
2. Chlamydia trachomatis ELISpot + IgG/IgA antibodies
3. HSV1/2 ELISpot + IgG/IgA/IgM antibodies
4. CD3/ CD56/ CD57 cells

Lung cancer:

1. Chlamydia pneumoniae ELISpot + IgG/IgA antibodies
2. Mycoplasma pneumoniae ELISpot + IgG/IgA antibodies
3. CD3/ CD56/ CD57 cells

Angiogenic tumors:

1. Bartonella ELISpot
2. CD3/ CD56/ CD57 cells

Oesophageal cancer:

1. Mycoplasma pneumoniae ELISpot + IgG/IgA antibodies
2. CD3/ CD56/ CD57 cells

Breast cancer:

1. Bartonella Elisot
2. Mycoplasma pneumoniae ELISpot + IgG/IgA antibodies
3. CD3/ CD56/ CD57 cells

Cervical cancer:

1. Chlamydia trachomatis ELISpot + IgG/IgA antibodies
2. HSV1/2 ELISpot + IgG/IgA/IgM antibodies
3. CD3/ CD56/ CD57 cells

Agenda

- Herpes viruses, enteroviruses, and other species
- Associations of viruses with different health conditions:
  - Syndromes (ME/Fibromyalgia, etc.)
  - Autoimmune pathologies
  - Neurological conditions
  - Cancers
- **SARS-CoV-2/COVID-19 and viral reactivation**
- Testing techniques
- Checklists and other resources
- Therapies

"Epstein-Barr virus (EBV) reactivation resulting from the inflammatory response to coronavirus infection may be the cause of previously unexplained long COVID"

pathogens

MDPI

Article

Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation

Jeffrey E. Gold [1,*], Ramazan A. Okyay [2], Warren E. Licht [3] and David J. Hurley [4]

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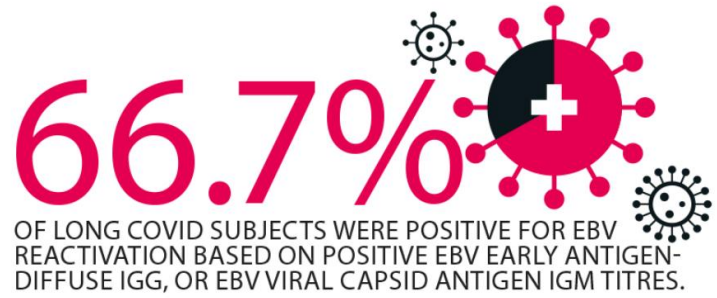
* Correspondence: jeff_gold@world.org

Abstract: Coronavirus disease 2019 (COVID-19) patients sometimes experience long-term symptoms following resolution of acute disease, including fatigue, brain fog, and rashes. Collectively these have become known as long COVID. Our aim was to first determine long COVID prevalence in 185 randomly surveyed COVID-19 patients and, subsequently, to determine if there was an association between occurrence of long COVID symptoms and reactivation of Epstein–Barr virus (EBV) in 68 COVID-19 patients recruited from those surveyed. We found the prevalence of long COVID symptoms to be 30.3% (56/185), which included 4 initially asymptomatic COVID-19 patients who later developed long COVID symptoms. Next, we found that 66.7% (20/30) of long COVID subjects versus 10% (2/20) of control subjects in our primary study group were positive for EBV reactivation based on positive titers for EBV early antigen-diffuse (EA-D) IgG or EBV viral capsid antigen (VCA) IgM. The difference was significant ($p < 0.001$, Fisher's exact test). A similar ratio was observed in a secondary group of 1
may occur soon afte
long COVID sympto
COVID-19 inflamma

check for updates

Citation: Gold, J.E.; Okyay, R.A.; Licht, W.E.; Hurley, D.J. Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. *Pathogens* **2021**, *10*, 763. https://doi.org/10.3390/



Lead study author Jeffrey E Gold said: "We ran EBV antibody tests on recovered COVID-19 patients, comparing EBV reactivation rates of those with long COVID symptoms to those without long COVID symptoms. The majority of those with long COVID symptoms were positive for EBV reactivation, yet only 10% of controls indicated reactivation.

… In a subset of 68 COVID-19 patients randomly selected from those surveyed, 66.7% of long COVID subjects versus 10% of controls were positive for EBV reactivation based on positive **EBV early antigen**-diffuse **IgG**, or **EBV viral capsid antigen IgM** titres."

Source: https://thebiomedicalscientist.net/news/long-covid-linked-epstein-barr-virus, https://www.mdpi.com/2076-0817/10/6/763

It also works the other way round: EBV increases susceptibility to infection by SARS-CoV-2

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VIRUS-CELL INTERACTIONS

Epstein-Barr Virus Lytic Replication Induces ACE2 Expression and Enhances SARS-CoV-2 Pseudotyped Virus Entry in Epithelial Cells

Dinesh Verma,[a] Trenton Mel Church,[a] Sankar Swaminathan[a,b]

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[b]Division of Microbiology and Immunology, Department of Pathology, University of Utah School of Medicine, Salt Lake City, Utah, USA

ABSTRACT Understanding factors that affect the infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is central to combatting coronavirus disease 2019 (COVID-19). The virus surface spike protein of SARS-CoV-2 mediates viral entry into cells by binding to the ACE2 receptor on epithelial cells and promoting fusion. We found that Epstein-Barr virus (EBV) induces ACE2 expression when it enters the lytic replicative cycle in epithelial cells. By using vesicular stomatitis virus (VSV) particles pseudotyped with the SARS-CoV-2 spike protein, we showed that lytic EBV replication enhances ACE2-dependent SARS-CoV-2 pseudovirus entry. We found that the ACE2 promoter contains response elements for Zta, an EBV transcriptional activator that is essential for EBV entry into the lytic cycle of replication. Zta preferentially acts on methylated promoters, allowing it to reactivate epigenetically silenced EBV promoters from latency. By using promoter assays, we showed that Zta directly activates methylated ACE2 promoters. Infection of normal oral keratinocytes with EBV leads to lytic replication in some of the infected cells, induces ACE2 expression, and enhances SARS-CoV-2 pseudovirus entry. These data suggest that subclinical EBV replication and lytic gene expression in epithelial cells, which is ubiquitous in the human population, may enhance the efficiency and extent of SARS-CoV-2 infection of epithelial cells by transcriptionally activating ACE2 and increasing its cell surface expression.

IMPORTANCE SARS-CoV-2, the coronavirus responsible for COVID-19, has caused a pandemic leading to millions of infections and deaths worldwide. Identifying the factors governing susceptibility to SARS-CoV-2 is important in order to develop strategies to prevent SARS-CoV-2 infection. We show that Epstein-Barr virus, which infects

"Epstein-Barr virus, which infects and persists in 90% of adult humans, **increases susceptibility of epithelial cells to infection by SARS-CoV-2**. EBV, when it reactivates from latency or infects epithelial cells, increases expression of ACE2, the cellular receptor for SARS-CoV-2, enhancing infection by SARS-CoV-2. Inhibiting EBV replication with antivirals may therefore decrease susceptibility to SARS-CoV-2 infection.

Source: *https://journals.asm.org/doi/pdf/10.1128/JVI.00192-21/*

COVID-19 can potentially cause reactivation of VZV

CASE

COVID-19 Associated With Concomitant Varicella Zoster Viral Encephalitis

Pavan Patel, DO, Anishee Undavia, MD, Rabia Choudry, MD, Yan Zhang, MD, and Aparna M. Prabhu, MD, MRCP

Neurology: Clinical Practice April 2021 vol. 11 no. 2 e219-e221 doi:10.1212/CPJ.0000000000000902

Correspondence
Dr. Patel
Patelpav@einstein.edu

Coronavirus disease 2019 (COVID-19) is a novel infectious disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Patients can be asymptomatic or symptomatic with severity determined by age and comorbid conditions. Common early symptoms are fever, cough, dyspnea, myalgia, headache, and diarrhea. In addition to respiratory complications, other systems involved include genitourinary, gastrointestinal, and cardiac.[1]

Neurologic complications such as encephalopathy were initially presumed to be because of multisystem involvement. Retrospective studies of patients with COVID-19 demonstrated multiple neurologic complications affecting central and peripheral nervous systems including dizziness, headache, hypogeusia, hyposmia, ischemic/hemorrhage stroke, and Guillain-Barre syndrome.[2] There was a single case report of hemorrhagic necrotizing encephalopathy reported in COVID-19, with imaging features of enhancement of bilateral thalami and medial temporal lobes.[3] To our knowledge, there have been no cases reported of coinfection with another virus during active COVID-19 infection resulting in neurologic manifestations.

PRACTICAL IMPLICATIONS

COVID-19 can potentially cause reactivation of VZV and subsequently have an additive effect in neurologic complications.

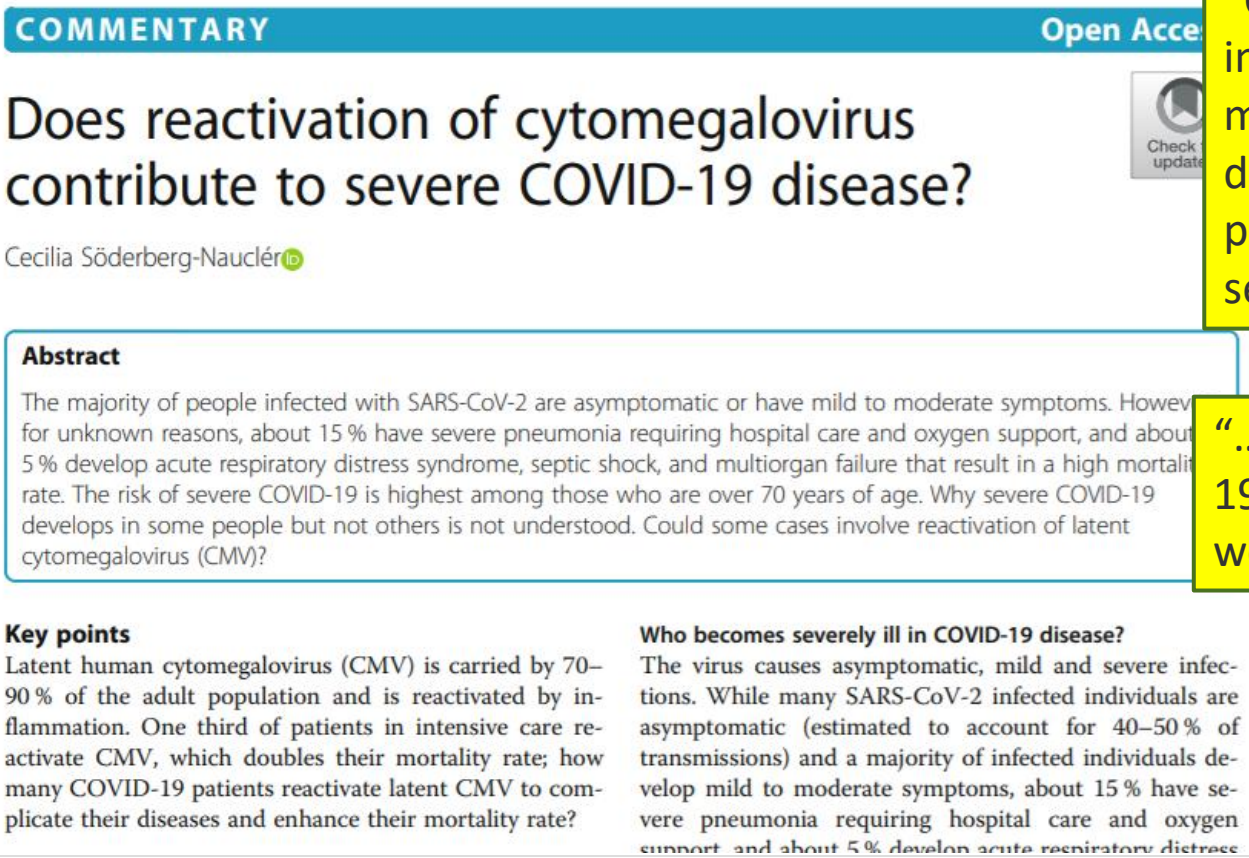
MORE ONLINE

COVID-19 Resources
For the latest articles, invited commentaries, and blogs from physicians around the world
NPub.org/COVID19

COVID-19 can potentially cause reactivation of VZV and subsequently have an additive effect in neurologic complications

Source: https://cp.neurology.org/content/neurclinpract/11/2/e219.full.pdf; https://www.rheumatologyadvisor.com/home/general-rheumatology/herpes-zoster-reactivation-covid19-vaccination-autoimmune-inflammatory-rheumatic/

Cytomegalovirus and Covid-19



COMMENTARY Open Acce

Does reactivation of cytomegalovirus contribute to severe COVID-19 disease?

Cecilia Söderberg-Nauclér

Abstract

The majority of people infected with SARS-CoV-2 are asymptomatic or have mild to moderate symptoms. Howev for unknown reasons, about 15 % have severe pneumonia requiring hospital care and oxygen support, and about 5 % develop acute respiratory distress syndrome, septic shock, and multiorgan failure that result in a high mortali rate. The risk of severe COVID-19 is highest among those who are over 70 years of age. Why severe COVID-19 develops in some people but not others is not understood. Could some cases involve reactivation of latent cytomegalovirus (CMV)?

Key points

Latent human cytomegalovirus (CMV) is carried by 70–90 % of the adult population and is reactivated by inflammation. One third of patients in intensive care reactivate CMV, which doubles their mortality rate; how many COVID-19 patients reactivate latent CMV to complicate their diseases and enhance their mortality rate?

Who becomes severely ill in COVID-19 disease?

The virus causes asymptomatic, mild and severe infections. While many SARS-CoV-2 infected individuals are asymptomatic (estimated to account for 40–50 % of transmissions) and a majority of infected individuals develop mild to moderate symptoms, about 15 % have severe pneumonia requiring hospital care and oxygen support, and about 5 % develop acute respiratory distress

"CMV reactivation and virus induced immune dysfunction may be under-estimated as a driver of immuno-pathogenesis in patients with severe COVID-19."

"… diagnosing CMV in COVID-19 patients could be well worth the effort."

Source: *Söderberg-Nauclér, C. Does reactivation of cytomegalovirus contribute to severe COVID-19 disease?. Immun Ageing* ***18,*** *12 (2021). https://doi.org/10.1186/s12979-021-00218-z*

Herpes Simplex Virus reactivation with COVID-19

microorganisms

MDPI

Article

Herpes Simplex Virus Re-Activation in Patients with SARS-CoV-2 Pneumonia: A Prospective, Observational Study

Erica Franceschini [1,*], Alessandro Cozzi-Lepri [2], Antonella Santoro [1], Erica Bacca [3], Guido Lancellotti [3], Marianna Menozzi [1], William Gennari [4], Marianna Meschiari [1], Andrea Bedini [1], Gabriella Orlando [1], Cinzia Puzzolante [1], Margherita Digaetano [1], Jovana Milic [3], Mauro Codeluppi [5], Monica Pecorari [4], Federica Carli [1], Gianluca Cuomo [1], Gaetano Alfano [6], Luca Corradi [1], Roberto Tonelli [7], Nicola De Maria [8], Stefano Busani [9], Emanuela Biagioni [9], Irene Coloretti [9], Giovanni Guaraldi [3], Mario Sarti [4], Mario Luppi [10], Enrico Clini [7], Massimo Girardis [9], Inge C. Gyssens [11,12] and Cristina Mussini [1,3,*]

"Conclusions: our study shows a high incidence of HSV-1 re-activation both virologically and clinically in patients with SARS-CoV-2 severe pneumonia"

Our study has some strengths: it is the first study that analyzed the incidence and clinical implications of HSV-1 re-activation in patients with SARS-CoV-2 pneumonia; second it has strong clinical and therapeutic implications for COVID-19 patients, especially in the present and future waves of hospitalized patients most of whom are treated with steroids, which is now considered the SOC.

In conclusion, our study shows a high incidence of both virological and clinical HSV-1 re-activation in patients with SARS-CoV-2 severe/critical pneumonia. Data show an association between this risk and treatment with steroids, which could not be explained by age, previous IMV, and level of inflammation at hospital admission. Further studies are needed, especially a randomized controlled trial, to confirm the utility of acyclovir prophylaxis in COVID-19 patients with severe pneumonia admitted to the hospital.

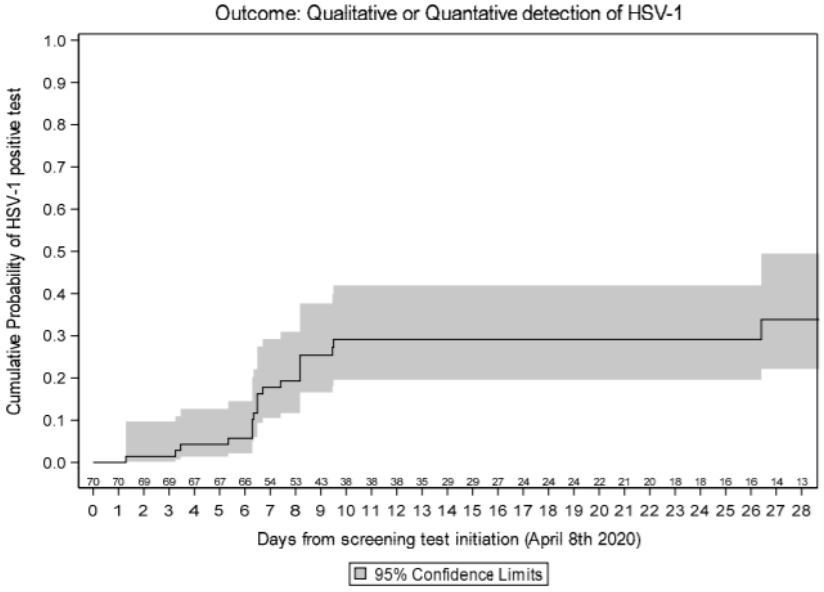


Figure 1. Kaplan–Meier estimates of HSV re-activation.

Source: *https://www.msd-animal-health.ie/species/dogs/ticks/*

Cytomegalovirus (CMV) can reactivate with COVID too …

CMV EliSpot

1 CMV Lytisch ! 22 SI
0-1 = negative
2-3 = weak positive
> 3 = positive

1 CMV Latent ! 2 SI
0-1 = negative
2-3 = weak positive
> 3 = positive

The result of the EliSpot test indicates current activity against Cytomegalo Virus (CMV).

Nov. 2021, before COVID diagnosis

CMV EliSpot

1 CMV lytic ! 355 SI
0-1 = negative
2-3 = weak positive
> 3 = positive

1 CMV Latent ! 106 SI
0-1 = negative
2-3 = weak positive
> 3 = positive

The result of the EliSpot test indicates current celluar activity against Cytomegalo Virus (CMV).

April 2022, after COVID

Source: ArminLabs results

… as well as Coxsackie and Echovirus

Coxsackie-Virus antibodies				
Coxsackie-Virus-IgG Type A7 (IFT)	+	1:3200	Titer	< 1:100
Coxsackie-Virus-IgG Type B1 (IFT)	+	1:3200	Titer	< 1:100
Coxsackie-Virus-IgA Type A7 (IFT)	+	1:320	Titer	< 1:10
Coxsackie-Virus-IgA Type B1 (IFT)	+	1:320	Titer	< 1:10

Echo IgG-/IgA-antibodies

6	**ECHO IgG-antibodies (IFT)**	**+**	**1:100**	**< 1:100**	**[..... *>**
6	**ECHO IgA-antibodies (IFT)**	**+**	**1:100**	**< 1:10**	**[..... *>**

The specific positive ECHO-virus-IgG/IgA-antibodies indicate current humoral immune responses against ECHO-virus (recent infection with ECHO-virus?).

Agenda

- Herpes viruses, enteroviruses, and other species
- Associations of viruses with different health conditions:
  - Syndromes (ME/Fibromyalgia, etc.)
  - Autoimmune pathologies
  - Neurological conditions
  - Cancers
- SARS-CoV-2/COVID-19 and viral reactivation
- **Testing techniques**
- Checklists and other resources
- Therapies

Testing can be either via antibodies, EliSpots, or PCR

The Humoral System: Antibody testing.
Antibody testing, often called serology, tests the B cell response. This consists of IgG (Immunoglobulin G), IgM (Immunoglobulin M), and (wherever possible) IgA (Immunoglobulin A).

The Cellular System: T-Cell immunity.
A technique for testing the other arm of the immune system, i.e., cellular T-cell immunity, is called EliSpot (enzyme-linked immunospot assay). This is a lymphocyte transformation test using an Interferon Gamma Release Assay.

PCR testing is available for all viruses, but is not as highly recommended in most cases as the two techniques above

Highly sensitive antibody tests available for all viruses (and other pathogens)

- E.g. EBV Immunoarray with 9 markers including viral capsid antigen (VCA), early antigen (EA), Epstein-Barr Nuclear Antigen (EBNA)
- Antibody tests including IgA (shows active infection along the mucosal membranes) for many of the viruses

Example: Varicella Zoster Virus (VZV)

VZV IgG-/IgA-/IgM-Antikörper

1 VZV-IgG positiv
4399,8 IE/l

<80 IE/l negativ
>80 - < 110 IE/l grenzwertig
>110 IE/l positiv

1 VZV-IgA positiv
2,032 Ratio

Ratio < 0,8 = negativ
Ratio 0,8 - 1,1 = grenzwertig
Ratio >= 1,1 = positiv

1 VZV-IgM negativ
0,186 Ratio

Ratio < 0,8 = negativ
Ratio 0,8 - 1,1 = grenzwertig
Ratio >= 1,1 = positiv

Serologisch Hinweis auf eine Infektion mit Varizella Zoster Virus (Varizella Zoster Virus Infektion? Herpes Zoster?). Wir empfehlen eine Verlaufskontrolle der VZV-Antikörper sowie die Bestimmung der aktuellen zellulären Aktivität mittels VZV-EliSpot in ca. 2-3 Wochen.

EBV immunoarray showing positive early antigen (EA) p54 IgG and IgM as well as +ve VCA IgG

Epstein-Barr-Virus Immuno-Array

EBV VCA p18 IgG	+	positive	negative
EBV VCA p23 IgG	+	positive	negative
EBV EA p54 IgG		negative	negative
EBV EA p138	+	positive	negative
EBV EBNA-1 IgG	+	positive	negative
EBV VCA p18 IgM		negative	negative
EBV VCA p23 IgM		negative	negative
EBV EA p54 IgM	+	positive	negative
EBV EA p138 IgM		negative	negative

The specific EBV-IgG/IgM-, EBV-Early Antigen-antibodies and EBV-EBNA-antibodies indicate humoral immune response against Epstein Barr Virus (former or reactivated or EBV-infection in convalescence?).

Source: https://pubmed.ncbi.nlm.nih.gov/32928810/

The Elispot technique reflects the current T-cellular activity of bacteria and viruses

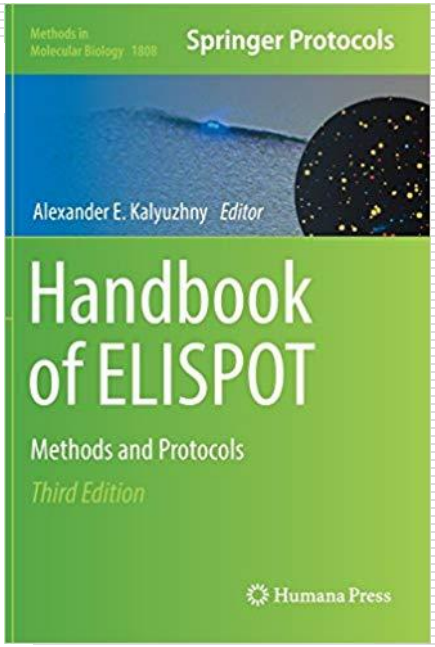
Chapter 1

Unique Strengths of ELISPOT for T Cell Diagnostics

Paul V. Lehmann and Wenji Zhang

Abstract

The T cell system plays an essential role in infections, allergic reactions, tumor and transplant rejection, as well as autoimmune diseases. It does so by the selective engagement of different antigen-specific effector cell lineages that differentially secrete cytokines and other effector molecules. These T cell subsets may or may not have cytolytic activity, can preferentially migrate to different tissues, and display variable capabilities to expand clonally. The quest of T cell immune diagnostics is to understand which specific effector function and T cell lineage is associated with a given clinical outcome, be it positive or adverse. No single assay can measure all of the relevant parameters. In this chapter, we review the unique contributions that ELISPOT assays can make toward understanding T cell-mediated immunity. ELISPOT assays have an unsurpassed sensitivity in detecting low frequency antigen-specific T cells that secrete effector molecules, including granzyme and perforin. They provide robust, highly reproducible data – even by first time users. Because
cytometry, ELISPOT is ideally su
ditions. These include defining (
establishing the fine–specificity
concentrations of the antigen in se
secretory products released by T
because T cells survive ELISPOT



"The quantification of single cell interferon-gamma (IFN-γ) release for assessing cellular immune responses using the Enzyme-linked immunospot (ELISPOT) assay is an invaluable technique in immunology."[1]

Source: 1 Sedegah M. The Ex Vivo IFN-γ Enzyme-Linked Immunospot (ELISpot) Assay Methods Mol Biol. 2015;1325:197-205; Humana Press; 3rd ed. 2018 edition (14 July 2018)

Enzyme-linked immunosorbent spots (Elispots) are available for most viruses: T-cells/cellular response

EBV EliSpot (lytic+latent)

1 EBV EliSpot (lytic) **!** **657 SI**

0-1 = negative
2-3 = weak positive
> 3 = positive

1 EBV EliSpot (latent) **!** **65 SI**

0-1 = negative
2-3 = weak positive
> 3 = positive

The result of the EliSpot test indicates current celluar activity against Epstein-Barr-Virus (EBV).

Explanation of EBV antigens:
EBV-lytic antigen: sign for replication of infectious EBV virions
EBV-latent antigen: sign for EBV latency with no production of infectious EBV virions

Positive above 1:
2-3 is weak positive
Over 3 is positive

Very high lytic levels seen post COVID

Source: https://pubmed.ncbi.nlm.nih.gov/32928810/

Herpes viruses: EBV, CMV (HSV1/2, VZV, HHV-6/HHV-7)

Analysis		Result	Units	Reference Range
EBV EliSpot (lytic+latent)				
1 **EBV EliSpot (lytic)**	!	16	SI	
0-1 = negative				
2-3 = weak positive				
> 3 = positive				
1 **EBV EliSpot (latent)**	!	8	SI	
0-1 = negative				
2-3 = weak positive				
> 3 = positive				

The result of the EliSpot test indicates current celluar activity against Epstein-Barr-Virus (EBV).

Explanation of EBV antigens:
EBV-lytic antigen: sign for replication of infectious EBV virions
EBV-latent antigen: sign for EBV latency with no production of infectious EBV virions

Cytomegalo Virus EliSpot

CMV-EliSpot	+	289	SI

>3 = positive
2-3 = weak positive
<2 = negative

The result of the EliSpot-Test is an indication for a current cellular activity against Cytomegalo-Virus.

EBV / CMV and SLE (Lupus): Clinical example

Untersuchung	Ergebnis	Einheit	Normbereich	Grafik
Autoantikörper				
4 **Antinukl. Antikörper/ANA (IFT~+**	**1:3200**		**< 1:100**	[..... *>
4 ANA-Fluoreszenzmuster~	homogen			

Nachweis von antinukleären Autoantikörpern. Der positive ANA-Nachweis kann als e i n Diagnosekriterium für einen Systemischen Lupus Erythematodes herangezogen werden. Dieser Befund kann auch bei anderen Autoimmunerkrankungen (weitere Kollagenosen, chronische aktive Hepatitis, Rheumatoide Arthritis u.ä.) beobachtet werden.
Die Untersuchung auf Autoantikörper gegen dsDNS und ENA ist bei klinischem Kollagenoseverdacht angezeigt! Bei ANA mit homogenem Muster und V.a. Rheumatoide Arthritis ist die Bestimmung des Rheumafaktors und der CCP-Antikörper sinnvoll.

EBV EliSpot (lytisch+latent)			
1 **EBV-lytischer Peptidmix**	!	**2**	**SI**
0-1 = negativ			
2-3 = grenzwertig			
ab 4 = positiv			
1 **EBV-latenter Peptidmix**	!	**9**	**SI**
0-1 = negativ			
2-3 = grenzwertig			
ab 4 = positiv			

Mittels EliSpot finden sich aktuell positive T-Zell-Reaktionen gegen Epstein Barr Virus (EBV).

Erläuterung EBV-Antigene:
EBV lytisches Antigen: Hinweis auf EBV-Replikation
EBV latentes Antigen: Hinweis auf EBV-Latenz

Achtung: Ab 01.08.2016 geänderte Nachweisgrenze!

CMV EliSpot			
1 **CMV Peptidmix**	!	**21**	**SI**
0-1 = negativ			
2-3 = grenzwertig			
ab 4 = positiv			

T-Cell testing – EliSpot – is available for:

- Borrelia burgdorferi (3 subspecies: B.b. sensu stricto + B.b. garinii + B.b. afzelii)
- Borrelia myamotoi
- Bartonella
- Babesia
- Chlamydia pneumoniae and trachomatis
- Mycoplasma pneumoniae
- Ehrlichia/Anaplasma
- Yersinia enterocolitica
- **Epstein Barr Virus (EBV): lytic and latent**
- **Cytomegalovirus (CMV): lytic and latent**
- **Herpes Simplex Virus 1 / 2**
- **Varicella Zoster Virus (VZV)**
- **HHV-6, HHV-7, HHV-8**

Also:
Candida
Aspergillus niger

Agenda

- Herpes viruses, enteroviruses, and other species
- Associations of viruses with different health conditions:
  - Syndromes (ME/Fibromyalgia, etc.)
  - Autoimmune pathologies
  - Neurological conditions
  - Cancers
- SARS-CoV-2/COVID-19 and viral reactivation
- Testing techniques
- **Checklists and other resources**
- Therapies

Checklists help decide which infections to test for; history and physical signs/symptoms also vital (1/2)

Coinfections-Checklist

Name, first name ..... Date (DD/MM/YYYY) .....

	Actual and former symptoms Please mark with a cross	X	Score-Points (filled in by physician/naturopath)	Ranking
1	Stomach ache, gut problems	☒	Ehrlichia&Anaplasma: 5	4
2	Anaemia	☐	Babesia: 4	5
3	Diarhoea intermittent	☐	Rickettsia: 4	5
4	Fever or feverish feeling	☒	Bartonella: 7	2
5	Lack of concentration, memory disturbance, forgetfulness	☒	Chl.pneumoniae: 6	3
6	Encephalitis/Inflammation of the brain (NMR)	☐	Chl.trachomatis: 2	7
7	Yellowish colour of the skin/eyes	☐	Yersinia: 3	6
8	Painful joints, swollen joints	☐	Mycoplasma: 5	4
9	General aches and pains, tendon problems	☐	Coxsackie-/Echo-Virus: 8	1
10	Flu-like symptoms intermittent	☒	EBV/CMV/HSV/VZV: 8	1
11	Rash(es)	☒		
12	Small red/purple spots of the skin	☐		
13	Heart problems, disturbance of cardiac rhythm	☒		
14	Cough, expectoration	☐		
15	Headache	☒		
16	Impaired liver function/ liver laboratory values	☒		
17	Pneumonia, bronchitis	☐		
18	Swollen lymph nodes	☒		
19	Tonsilitis	☒		
20	Enlargement of the spleen	☐		

Post-Covid checklist also available (2/2)

Post Covid Coinfection checklist

Name, first name ..... Date (DD/MM/YYYY) .....

	Your current and former symptoms Please click on the boxes next to the symptoms that you suffer from	X
1	Stomach ache, gut problems	
2	Anaemia	
3	Diarhoea intermittent, intestinal crampings/pain	
4	Fever or feverish feeling	
5	Lack of concentration, memory loss, forgetfulness	
6	Encephalitis/Inflammation of the brain	
7	Yellowish colour of the skin/eyes	
8	Painful joints or swollen joints	
9	General aches and pains, tendon problems	
10	Flu-like symptoms	
11	Rash(es), striae, exanthema	
12	Small red/purple spots of the skin	
13	Heart problems, feeling disturbance cardiac rhythm	
14	Cough, expectoration, "air-hunger"	
15	Headache, dizziness	
16	Impaired liver function/ liver laboratory values	
17	Pneumonia, bronchitis	
18	Swollen lymph nodes	
19	Enlargement of the spleen	
20	Fatigue / exhaustion, intermittent or chronic CFS	
21	Muscle pain, muscle weakness	
22	Shivering, chill	
23	Blurred, foggy, cloudy, flickering, double vision	
24	Nausea, vomiting	
25	Dark urine	
26	Itching or pain when urinating	
27	Tingling, numbness, "burning" sensations	
28	Neck pain, neck stiffness	
29	Shoulder pain	

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Zirbelstr. 58
86154 Augsburg
GERMANY

30	Back pain, pelvic pain	
31	Sleeplessness	
32	Night sweat, sometimes between 2 and 4 a.m.	
33	Sore throat, throat pain	
34	Tinnitus, hearing loss	
35	Dry skin	
36	Conjunctivitis, inflammation of the eyes	
37	Panik attacks, depression, psychosis, mood swings	
38	Seizures, tremors	
39	Sinusitis	

Below you'll find the number of the symptoms for each of the infections that we test for and the ranking, in which order you should test for them

Ranking of the infections	No. of symptoms	Rank
Chlamydia pneumoniae		
Chlamydia trachomatis		
Mycoplasma pneumoniae		
Yersinia		
Campylobacter		
H. pylori		
HSV 1/2		
EBV		
CMV		
VZV		
HHV 6		
Parvovirus		
Coxsackie-Virus		
Echovirus		
Candida		
Aspergillus		
Parasites		

Electronic version fills automatically

Coinfections-Checklist

Name, first name ..... Date (DD/MM/YYYY) .....

	Actual and former symptoms Please mark with a cross	X	Score-Points (filled in by physician/naturopath)	Ranking
1	Stomach ache, gut problems	☒	Ehrlichia: 7	3
2	Anaemia	☐	Babesia: 4	6
3	Diarhoea intermittent	☐	Rickettsia: 6	4
4	Fever or feverish feeling	☒	Bartonella: 8	2
5	Lack of concentration, memory disturbance, forgetfulness	☒	Chl.pneumoniae: 9	1
6	Encephalitis/Inflammation of the brain (NMR)	☐	Chl.trachomatis: 5	5
7	Yellowish colour of the skin/eyes	☐	Yersinia: 5	5
8	Painful joints, swollen joints	☒	Mycoplasma: 7	3
9	General aches and pains, tendon problems	☒	Coxsackie-Virus: 9	1
10	Flu-like symptoms intermittent	☒	EBV/CMV/HSV: 7	3
11	Rash(es)	☒		
12	Small red/purple spots of the skin	☐		
13	Heart problems, disturbance of cardiac rhythm	☒		
14	Cough, expectoration	☐		
15	Headache	☒		
16	Impaired liver function/ liver laboratory values	☐		
17	Pneumonia, bronchitis	☐		
18	Swollen lymph nodes	☒		
19	Tonsilitis	☐		
20	Enlargement of the spleen	☐		
21	Fatigue / exhaustion, intermittent or chronic CFS	☒		
22	Muscle pain, muscle weakness	☒		
23	Shivering, chill	☐		
24	Blurred, foggy, cloudy, flickering, double vision	☒		
25	Nausea, vomiting	☒		
26	Dark urine	☐		
27	Itching or pain when urinating	☐		

Ranked in order of priority – draw for first place here: Chlamydia pneumoniae (CPN) and Coxsackie

Tailored testing protocols (examples)

» Cardiac Dysrrhythmias:

1. CMV ELISpot + IgG/IgM antibodies
2. EBV ELISpot + IgG/IgM antibodies
3. HSV 1/2 IgG/IgA/IgM antibodies
4. Coxsackie Virus IgG/IgA antibodies
5. Echovirus IgG/IgA antibodies
6. Rickettsia ELISpot
7. Borrelia ELISpot

» Uveitis:

1. Borrelia ELISpot
2. Tickplex basic
3. CD3/ CD56/ CD57 cells
4. Borrelia ELISpot
5. VZV ELISpot + IgG/IgA/ IgM antibodies
6. HSV1/2 ELISpot + IgG/ IgA/IgM antibodies
7. CMV ELISpot
8. Bartonella ELISpot
9. Chlamydia trachomatis ELISpot + IgG/IgA antibodies

» Skin rashes eg maculopapular exanthemata:

1. HHV-7ELISpot
2. Coxsackie Virus IgG/IgA antibodies
3. Echovirus IgG/IgA antibodies

» Rheumatoid Arthritis

1. Borrelia ELISpot
2. CD3/ CD56/ CD57 cells
3. Coxsackie Virus IgG/IgA antibodies
4. Echovirus IgG/IgA antibodies
5. Yersinia ELISpot
6. Campylobacter IgG/IgA antibodies
7. EBV ELISpot
8. CMV ELISpot
9. Mycoplasma pneumoniae IgG/ IgA antibodies
10. Chlamydia pneumoniae IgG/ IgA antibodies

Agenda

- Herpes viruses, enteroviruses, and other species
- Associations of viruses with different health conditions:
  - Syndromes (ME/Fibromyalgia, etc.)
  - Autoimmune pathologies
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Herbs and nutraceuticals for viral infections (1/2)

Herpes, especially Epstein Barr, Cytomegalovirus, Varicella Zoster virus

Liquorice: Its component glycyrrhizin is particularly responsible for its antiviral activity; "novel way to interrupt latency" of EBV[1]

Andrographis paniculata: Andrographolide, the active extract from plants of the Andrographis genus, has broad-spectrum antiviral properties: "miraculous compound to restrain virus replication and virus-induced pathogenesis … shown to inhibit transcription of EBV IE genes and the production of EBV virions"[2]

Scullcap/Baicalein: Noted antiviral properties, also against Coxsackie[3]

Dandelion: Blocks the interaction between ACE2 cell surface receptor and SARS-CoV-2 spike protein[4]

Artemisia annua: "Artemisia annua L. extracts inhibit the *in vitro* replication of SARS-CoV-2 and two of its variants."[5] "…the bioactivity of artemisinin and its semisynthetic derivative artesunate is even broader and includes the inhibition of certain viruses, such as human cytomegalovirus and other members of the *Herpesviridae* family (e.g., herpes simplex virus type 1 and Epstein-Barr virus)"[6]

Sources: 1. https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC1052015/; 2. Gupta S et al. Broad-spectrum antiviral properties of andrographolide. Arch Virol. 2017 Mar;162(3):611-623; 2. Andrei G et al. Novel Therapeutics for Epstein-Barr Virus. Molecules. 2019 Mar 12;24(5):997; Lin, TP et al. Inhibition of the Epstein–Barr virus lytic cycle by andrographolide. Biol. Pharm. Bull. 2008, 31, 2018–2023; 3. Fu Q, Gao L, Fu X, Meng Q, Lu Z. Scutellaria baicalensis Inhibits Coxsackievirus B3-Induced Myocarditis Via AKT and p38 Pathways. J Microbiol Biotechnol. 2019 Aug 28; 4. https://www.biorxiv.org/content/10.1101/2021.03.19.435959v1.article-info; 5. https://www.sciencedirect.com/science/article/pii/S0378874121002439; 6. https://academic.oup.com/cid/article/47/6/804/325924. All images from Wikipedia, free to use on Commons License.

Herbs and nutraceuticals for viral infections (2/2)

Nigella sativa (Black Seed oil): Black Seed oil from Nigella sativa seeds has been found to act against seasonal allergic rhinitis, avian influenza and cytomegalovirus.[1, 2]. It has virucidal activity against herpes simplex[3]

Quercetin and **zinc:** Quercetin acts as an ionophore and carries the zinc deep into the cell[4]

Curcumin: Antiviral and immunomodulatory[5,] "improves mitochondrial dynamics regarding mitochondrial biogenesis and mitophagy"[6]

Cistus incanus tea – demonstrated antiviral action on several viruses, including SARS-CoV-2[7]

The amino acid L-Lysine appears to apply universally across the entire family of herpes viruses[8]

Support for immunity/natural killer cell activity:

Glutathione – liposomal; N-Acetyl Cysteine: precursor to GSH, mucolytic and perturbs SARS-CoV-2 spike protein conformation[9]; releases histamine however[10], beware with MCAS

Enzymatically modified rice bran

Sources: 1. https://pubmed.ncbi.nlm.nih.gov/23855426/; 2. https://pharmacologyonline.silae.it/files/newsletter/2019/vol2/ PhOL_2019_2_NL007_Molla.pdf; 3. https://www.sciencedirect.com/science/article/abs/pii/S0192056100000369?via%3Dihub; 4. https://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1001176; 5. *https://www.ncbi.nlm.nih.gov/labs/pmc/ articles/PMC7899028/; 6. de Oliveira MR et al. Curcumin, mitochondrial biogenesis, and mitophagy: Exploring recent data and indicating future needs. Biotechnol Adv. 2016;34(5):813-826; Ungvari, Z et al. (2011). 7. https://www.sciencepublishinggroup.com/journal/paperinfo?journalid =320&doi=10.11648/ j.jdmp.20210703.13; 8. https://www.researchgate.net/publication/344210822_Lysine_Therapy_for_SARS-CoV-2; 9.* https://chemrxiv.org/engage/apigateway/chemrxiv/assets/orp/resource/item/60c753ec4c89190f3bad43ca/original/n-acetyl-cysteine-a-tool-to-perturb-sars-co-v-2-spike-protein-conformation.pdf; 10. *https://pubmed.ncbi.nlm.nih.gov/2409763/; All images from Wikipedia, free to use on Commons License*

... as well as medicinal mushrooms to help the switch from Th2 to Th1

Iwatsuki et al. (2013) found **reishi inhibits the activation of Epstein-Barr virus.**[1]

Agaricus blazeii: anti-infectious properties "mediated through the mushroom's stimulation of innate immune cells, such as monocytes, NK cells, and dendritic cells, and the amelioration of a skewed Th1/Th2 balance and inflammation."[2]

Table 2

The list of introduced medicinal herbs and mushrooms. (+ stands for the level activity, representing mild, moderate, severe and very severe respectively).

Medicinal Herbs and Mushrooms	Antiviral Activity	Anti-Inflammatory Activity	Anticancer Activity
Prunella vulgaris	++	+++	++
Garlic (*Allium sativum*)	++	+	++
Zingiber officinalis	++	+++	+
Lentinus edodes mycelia (shiitake)	+++	+++	-
Grifola frondosa	++	+	++
Ganoderma lucidum aqueous extract (GLE)	+++	+++	-
Chlorella vulgaris ethanolic extract (CVE)	+++	+++	-
Inonotus obliquus	++	++++	++++

Open in a separate window

2. The Potential Use of Mushrooms and Herbs against SARS-CoV-2 Infection Go to:

3

*Source: 1. Iwatsuki, K et al. (December 2003). "Lucidenic acids P and Q, methyl lucidenate P, and other triterpenoids from the fungus Ganoderma lucidum and their inhibitory effects on Epstein-Barr virus activation". Journal of Natural Products. **66** (12): 1582–1585. 2.* Hetland G et al. The Mushroom Agaricus blazei Murill Elicits Medicinal Effects on Tumor, Infection, Allergy, and Inflammation through Its Modulation of Innate Immunity and Amelioration of Th1/Th2 Imbalance and Inflammation. Adv Pharmacol Sci. 2011 *3.* Shahzad F, Anderson D, Najafzadeh M. The Antiviral, Anti-Inflammatory Effects of Natural Medicinal Herbs and Mushrooms and SARS-CoV-2 Infection. Nutrients. 2020 Aug 25;12(9):2573. doi: 10.3390/nu12092573. PMID: 32854262; PMCID: PMC7551890.

Multiple flavonoids with antiviral activity ...

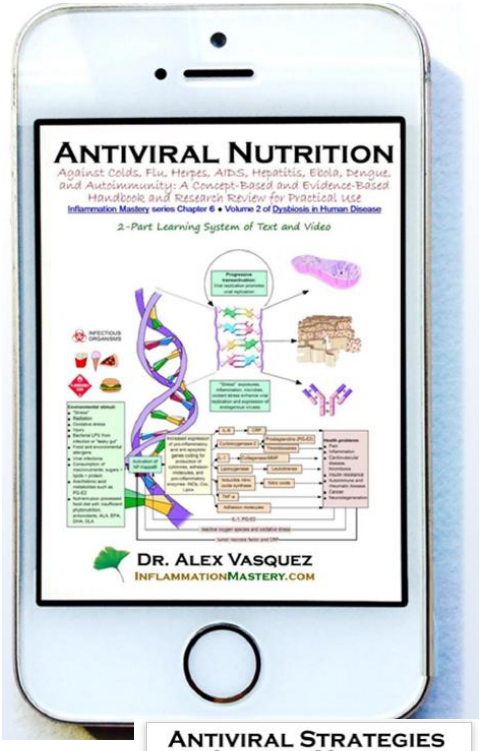
"... significant antiviral properties both in vitro and in vivo."

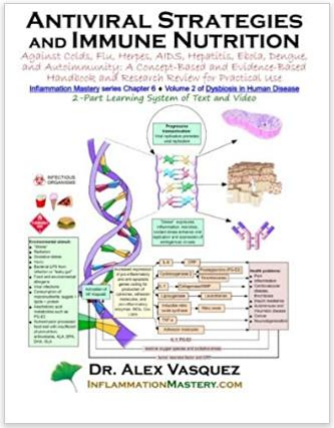
Table 1 The different viruses which inhibited by various flavonoids

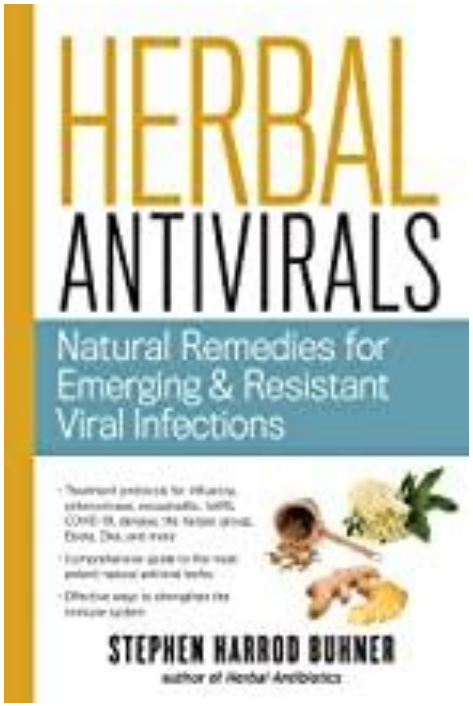
Viruses	Model	Flavonoids	References
Influenza virus	MDCK cells	Gallocatechin-7-gallate, catechins, apigenin, luteolin, 3-deoxysappanchalcone, scutellarin, galuteolin, vitexin, chrysin, kaempferol, quercetin, myricetin, rhamnocitrin, rutin, daidzein, genistein, sappanchalcone, baicalein, oroxylin A	Liu et al. [19], Yonekawa et al. [20]
HBV	Vero cells	Myricetin rhamnoside, myricetin-3-α-O-ramnosil (1→6)-α-galactoside, 5,3′-dihydroxy-3,6,7,8,4′- pentamethoxyflavone, 5-hydroxy-3,6,7,3′,4′- pentamethoxyflavone	Ortega et al. [21]
HCV	Huh-7.5 cells	Epigallocatechin gallate (EGCG), sorbifolin, pedalitin	Mekky et al. [22]
HIV-1	CD4⁺ NKT cells, T cells	Hesperidin, linarin, catechins, genistein, herbacitrin, naringin, formononetin, biochanin A	Nzuza et al. [23]
HIV-2	Vero cells	Genistein, formononetin, biochanin A	Patra [24]
HSV-1	Vero and CV1 cells	Catechins, genistein,gorvanol A, kaempferol, 5,6,7-trimethoxyflavone, 5,3′-dihydroxy-3,6,7,8,4′- pentamethoxyflavone, 5-hydroxy-3,6,7,3′,4′- pentamethoxyflavone, coumestrol, houttuynoid A, chrysin	Li et al. [25]
HSV-2	Vero cells	Genistein, coumestrol, houttuynoid A	Bús et al. [26]
HPV-1	Human condyloma, Vero cells	Catechins, 5,3′-dihydroxy-3,6,7,8,4′- pentamethoxyflavone, 5-hydroxy-3,6,7,3′,4′- pentamethoxyflavone	Patra [24]
DENV-2	C6/36 Aedes albopictus mosquito cell, hepatocytes (Huh-7)	Quercetin, quercitrin, kaempferitrin, chrysin	Patra [24]
Sendai virus (SeV)	Mice model	Baicalein	Dou et al. [27]
Zika virus (ZIKV)	Vero cells	Baicalein, baicalin, pinocembrin, chrysin, myricetin, luteolin, Epigallocatechin gallate, epicatechin gallate, gallocatechin gallate, quercetin-3-β-O-D-glucoside	Oo et al. [28]
CVB3	Vero cells	Mosloflavone, oroxylin A, norwogonin, epigallocatechin-3-gallate	Patra [24]
JEV	A549 cells, BHK21 cells	Epigallocatechin-3-gallate (EGCG), luteolin, kaempferol	Patra [24]
EBV	Ramos cells	Genistein, quercetin, apigenin, luteolin, baicalein	Granato et al. [29]
Poliovirus	Vero cells	5,6,7-Trimethoxyflavone, 3-methylkaempferol, 3(2H)-isoflavene	Ortega et al. [21]
RSV	Vero cells	Genistein, quercetin, baicalein, baicalin, epigallocatechin-3-gallate, proanthocyanidin	Zhang et al. [30]
Coronovirus	Vero cells	Quercetin, Luteolin, quercetin, quercetrin, kaempferol glycosides	Patra [24]
SARS-CoV	3CL protease activity assay	Daidzein, rutin, genistein, icaritin, genistin, ipriflavone, (−) gallocatechin, (±)-epigallocatechin gallate, puerarin, (−)-epicatechin, glabridin, (±)-catechin, baicalein, diosmin, diosmetin, skullcapflavone II, orientin, acacetin, bacicalin, rhoifolin, hispidulin, sinensetin, oroxin B, pectolinarin, cirsiliol, homoplantaginin, amentoflavone, luteolin, herbaacetin, kaempferol, morin, myricetin, fisetin, quercitrin, queretin, helichrysetin, cardamonin, neodesperidin dishydrochalcone, mangiferin, auraptene	Jo et al. [7]
Human CMV	HEL 299 cells	Genistein, 5,6,7-Trimethoxyflavone	Patra [24]
Rotavirus	MA-104 cells, Caco2 cells	Genistein, epigallocatechin Gallate (EGCG), α-glucosyl hesperitin (GH)	Lipson et al. [31]
Adenovirus	Hep2 cells, SW480 cell, BCC-1/KMC cells	Catechins, genistein, quercetin	Patra [24]
SARS-CoV-2	Vero cells	Baicalein, scutellarein, dihydromyricetin, quercetagetin, myricetin	Liu et al. [32]

Source: *Wang L, Song J, Liu A, Xiao B, Li S, Wen Z, Lu Y, Du G. Research Progress of the Antiviral Bioactivities of Natural Flavonoids. Nat Prod Bioprospect. 2020 Oct;10(5):271-283*

Many sources of information available







Download COVID-19: Nutraceutical and Botanical Recommendations Patient Education tools

As part of the Functional Medicine approach to COVID-19, IFM has outlined the biological plausibility, mechanism of action, strength of evidence, and risk of harm for various nutraceutical and botanical agents that may have activity against SARS-CoV-2. This article is part two of a series. Click here to view part one.

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Andrographis Paniculata	Melatonin
Astragalus Membranaceus	Mushrooms
Berberine	N-Acetylcysteine (NAC)
Beta Glucans	Quercetin
Curcumin	Resveratrol
Echinacea	Vitamin A
Elderberry	Vitamin C
Epigallocatechin Gallate (EGCG)	Vitamin D

THE INSTITUTE FOR FUNCTIONAL MEDICINE

COVID-19: Nutraceutical and Botanical Recommendations for Patients

Research on specific botanical and nutraceutical agents indicates they may have a role in the pre-exposure and early phase of COVID-19 based on their ability to improve the immune response to, and recovery from viral illnesses. Beneficial botanical and nutraceutical agents are listed below, along with dosing recommendations from your functional medicine practitioner. For more information on personalized recommendations, please consult your practitioner directly.

NUTRACEUTICAL OR BOTANICAL AGENT	BENEFITS	ENHANCES IMMUNE SYSTEM	DECREASES VIRAL GROWTH	REDUCES SYMPTOMS
Curcumin *500-1,000 mg, 2x daily*	Curcumin has been shown to reduce inflammation and decrease viral activity for COVID-19.	■	■	■
Quercetin *Regular: 1,000 mg orally, 2x daily Phytosome: 500 mg, 2x daily*	Quercetin is found in fruits and vegetables and has a wide range of benefits, including decreasing viral growth.	■	■	■
Zinc acetate, citrate, picolinate, or glycinate; zinc gluconate (as lozenge) *30-60 mg orally daily, in divided doses*	A large body of research shows that zinc has strong anti-viral properites against many viruses.	■	■	■
N-Acetylcysteine (NAC) *600-900 mg, 2x daily*	N-acetylcysteine promotes the production of glutathione, a potent antioxidant that supports immune function. It also reduces the severity of the flu.	■		■
Vitamin D *5,000 IU orally, daily*	Vitamin D enhances immune system function, reduces viral growth, and can reduce upper respiratory infections.	■	■	■
Vitamin A *10,000-25,000 IU, daily*	Vitamin A is anti-inflammatory, enhances immune function, and supports the lining of the respiratory tract.	■		■
Vitamin C *1-3 g orally, daily*	Vitamin C contributes to immune defense by supporting various cellular functions of the immune system. Vitamin C has been used in hospital ICUs to treat COVID-19 infection.	■	■	■

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NUTRACEUTICAL OR BOTANICAL AGENT	BENEFITS	ENHANCES IMMUNE SYSTEM	DECREASES VIRAL GROWTH	REDUCES SYMPTOMS
Melatonin *5-20 mg, taken at bedtime*	In addition to promoting restful sleep, melatonin has been shown to reduce inflammation.	■	■	
Elderberry (*Sambucus nigra*) *500 mg orally, daily*	Elderberry is packed with vitamin C, dietary fiber, and antioxidants. It has been used extensively in the prevention of influenza.	■	■	
Green tea or **epigallocatechin gallate**	In addition to reducing inflammation, green tea enhances the immune	■	■	■

Sources: https://www.ifm.org/news-insights/functional-medicine-approach-covid-19-additional-research-nutraceuticals-botanicals/; https://p.widencdn.net/kvdwlh/COVID-19_Nutraceutical-and-Botanical-Recommendations-for-Patients_v4; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190003/pdf/imcj-19-08.pdf

Structured strategies from Dr. Sam Yanuck and Dr. Fitzgerald

Figure 1. Five Targets of Support as they apply to the four Phases in the time course of disease. It's essential that if the patient moves from the Infection Phase to the Escalating Inflammation Phase, the emphasis shifts to downregulation of the potentially life-threatening inflammatory process.

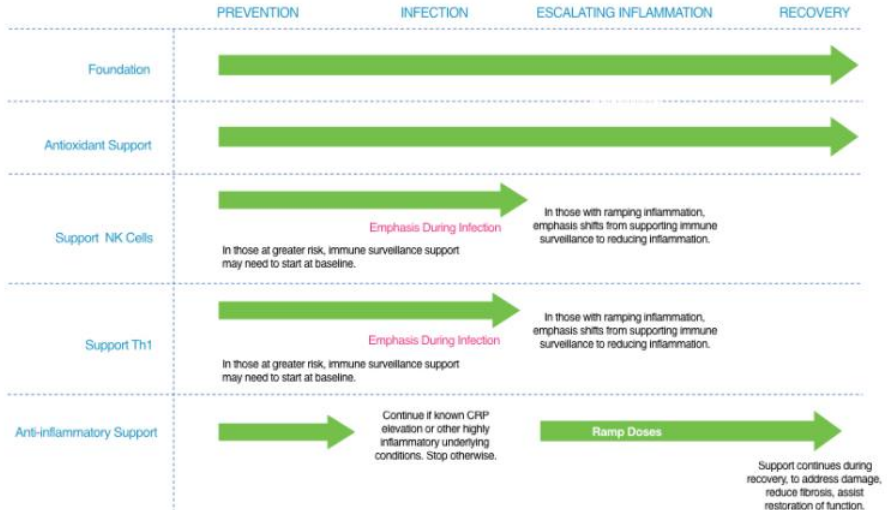
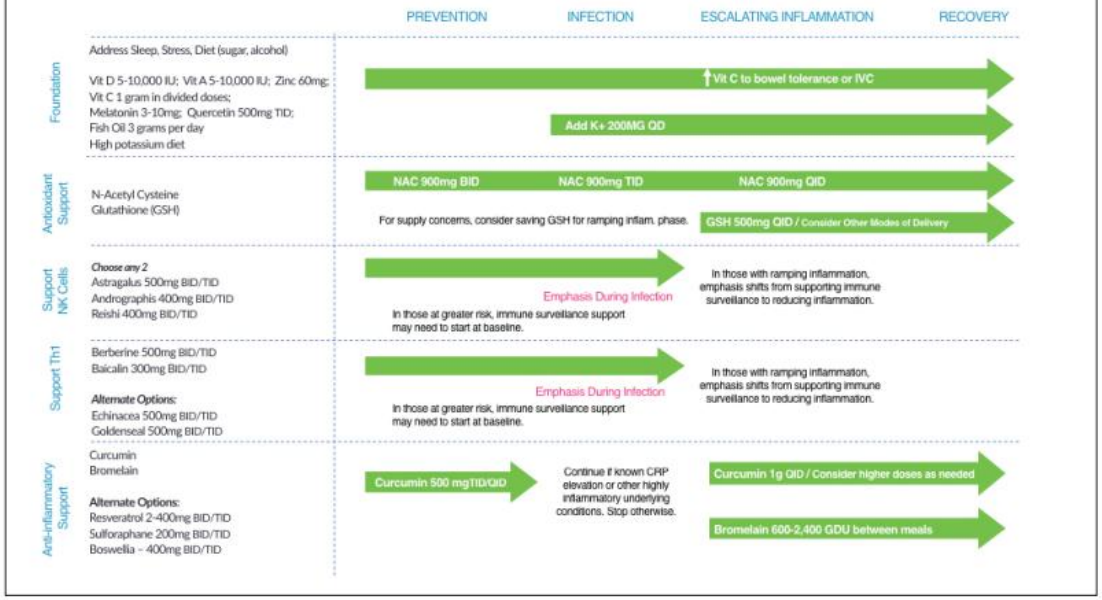


Figure 2. Proposed approach to populating the five Targets of Support, across the four Phases of COVID-19 disease.



REVIEW OF EMERGING RESEARCH

Evidence Supporting a Phased Immuno-physiological Approach to COVID-19 From Prevention Through Recovery

Yanuck SF[1], Pizzorno J[2], Messier H[3], Fitzgerald KN[4]

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[3]*Medical Director, Altum Medical; Chief Medical Officer, Medical Intelligence Learning Labs; San Francisco, CA, USA.*
[4]*Clinic Director, Sandy Hook Functional Medicine; Sandy Hook, CT, USA.*

Abstract

This paper presents an evidence-based strategy for improving clinical outcomes in COVID-19. ased on the phases of the disease, ntions for one phase may not be ferent phase. The four phases on, Infection, Inflammation and

ased approach is recognition of r two different components of infection and late stage severe o aspects of the disease suggest f clinical emphasis that seem on ntirely concordant. We describe peutic strategies and appropriate four main stages of disease -19.

in COVID-19 suggests that the both evade the innate immune phages. Delayed innate immune population of macrophages can a blunted antigen presentation, ing activation of the adaptive s, one clinical strategy involves e and adaptive immune responses se of illness, with the goal of improving the timeliness, readiness, and robustness of both the innate and adaptive immune responses.

At the other end of the disease pathology spectrum, risk of fatality in COVID-19 is driven by excessive and persistent upregulation of inflammatory mechanisms associated with cytokine storm. Thus, the second clinical strategy is to prevent or mitigate excessive inflammatory response to prevent the cytokine storm associated with high mortality risk.

Clinical support for immune system pathogen clearance mechanisms involves obligate activation of immune response components that are inherently inflammatory. This puts the goals of the first clinical strategy (immune activation) potentially at odds with the goals of the second strategy (mitigation of proinflammatory effects). This creates a need for discernment about the time course of the illness and with that, understanding of which components of an overall strategy to apply at each phase of the time course of the illness.

We review evidence from early observational studies and the existing literature on both outcomes and mechanisms of disease, to inform a phased approach to support the patient at risk for infection, with infection, with escalating inflammation during infection, and at risk of negative sequelae as they move into recovery.

Sources: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7190003/pdf/imcj-19-08.pdf

GP information leaflet available

Natural Antivirals
GP INFORMATION LEAFLET

Many natural remedies have shown proven antiviral activity. A selection are included below. Please also refer to the leaflets on Vitamin C, D and zinc.

Iodine has long been known as a universal antiseptic.[i, ii] Povidone-iodine "was effective against all the virus species tested," e.g. adeno-, mumps, rota-, polio- (types 1 and 3), coxsackie-, rhino-, herpes simplex, rubella, measles and influenza viruses.[iii, iv, v] A 100 ppm molecular iodine rinse exhibited "complete inactivation of SARS-CoV-2 at both 30 secs. and also at 60 secs."[vi] Dosage**:** Depends on type used, and thyroid status. Please refer to a health professional. Topical use for bites, stings etc, applied ad lib.

Liquorice has been used for its antiviral properties since antiquity.[vii] Its component glycyrrhizin is particularly responsible for its antiviral activity.[viii] It has been found effective against Hepatitis B[ix], C[x], herpes viruses, enteroviruses including Coxsackie (both A and B)[xi], [xii], RSV[xiii] and SARS-associated Coronavirus[xiv].Dosage: Depends on the form used, whether tincture or capsule. Please refer to intake instructions and a health professional

L-Lysine appears to apply universally across the entire family of herpes viruses.[xv], [xvi] L-Lysine has proven an especially effective agent for reducing the occurrence, severity and healing time for recurrent HSV infection.[xvii], [xviii] A September 2020 preprint found that ~ 80% of acute-stage Covid-19 sufferers given lysine displayed at least a 70% reduction in symptoms in the first 48 hours [xix]. Dosage up to 3g/day.

Garlic has evidenced antiviral activity on respiratory infections in multiple studies. [xx, xxi] It has shown anti-viral activity against the adenovirus family, the enteroviruses Coxsackie and Echovirus, as well as cytomegalovirus. [xxii, xxiii], [xxiv], [xxv, xxvi] A March 2020 article revealed the potential of garlic oil against SARS-CoV-2.[xxvii] Dosage: 2 to 5 g of fresh raw garlic; 0.4 to 1.2 g of dried garlic powder; 2 to 5 mg garlic oil; 300 to 1,000 mg of garlic extract (as solid material); 2,400 mg of aged garlic extract (liquid)/day.

Glutathione (GSH) & N-Acetyl Cysteine (NAC): GSH can provide protection from viruses such as herpes and influenza A [xxviii], [xxix]. Numerous other studies have demonstrated the antiviral properties of GSH and NAC, including some action against COVID-19 [xxx], [xxxi], [xxxii].Dosage: prevention, up to 2,500mg/day. Treatment, up to 6000mg/day.

Resveratrol has been found to inhibit the replication of influenza virus [xxxiii]. It has also shown efficacy both as an independent and adjunct therapy for Coronavirus as a viral replication blocker as well as prolonging cellular survival after virus infection [xxxiv], [xxxv], [xxxvi], [xxxvii], [xxxviii], [xxxix], [xl]. Dosage: Up to 500mg/day, depending on strength and purity.

Essential plant oils including **oregano** have shown encouraging antiviral properties, particularly against HSV-1[xli]. Oregano oil's primary active component, carvacrol, has proven effective against the norovirus and upper respiratory conditions including coronavirus [xlii], [xliii], [xliv]. Dosage: up to 600mg/day, depending on strength and purity.

Black Seed oil from Nigella sativa seeds have been found to act against seasonal allergic rhinitis, avian influenza and cytomegalovirus.[xlv], [xlvi], [xlvii] It has virucidal activity against herpes simplex and hepatitis C virus infections. [xlviii], [xlix]. Various compounds from Nigella sativa may potentially inhibit SARS-CoV-2 replication and attachment to host cell receptors.[l] Dosage: 1-2 tspns/day.

Andrographis paniculata has been used for centuries in the treatment and prevention of upper respiratory tract infections, coughs, and sinusitis. [li] *It has been shown, in vitro, to be* effective against avian influenza A (H9N2 and H5N1) and human influenza A H1N1 viruses. [lii] [liii] Andrographis is able to decrease the activity of furin protease, which can help prevent adhesion of SARS-CV-2 to mucosal epithelial cells. [liv] Dosage: Please refer to a health professional.

You must not rely on the information on our website as an alternative to medical advice from your doctor or other professional healthcare provider and if you have any specific questions about any medical matter, you should consult your doctor or other professional healthcare provider. Dosage guidance is general and more specific treatment amounts should again be obtained from a qualified health professional.

Please ask Gilian, gilian@aonm

Tailored testing protocols (examples)

Microbe-Disease correlations according to Armin Laboratories

arminlabs

» Cardiac Dysrrhythmias:

1. CMV ELISpot + IgG/IgM antibodies
2. EBV ELISpot + IgG/IgM antibodies
3. HSV 1/2 IgG/IgA/IgM antibodies
4. Coxsackie Virus IgG/IgA antibodies
5. Echovirus IgG/IgA antibodies
6. Rickettsia ELISpot
7. Borrelia ELISpot

» Uveitis:

1. Borrelia ELISpot
2. Tickplex basic
3. CD3/ CD56/ CD57 cells
4. Borrelia ELISpot
5. VZV ELISpot + IgG/IgA/ IgM antibodies
6. HSV1/2 ELISpot + IgG/ IgA/IgM antibodies
7. CMV ELISpot
8. Bartonella ELISpot
9. Chlamydia trachomatis ELISpot + IgG/IgA antibodies

» Skin rashes eg maculopapular exanthemata:

1. HHV-7ELISpot
2. Coxsackie Virus IgG/IgA antibodies
3. Echovirus IgG/IgA antibodies

» Rheumatoid Arthritis

1. Borrelia ELISpot
2. CD3/ CD56/ CD57 cells
3. Coxsackie Virus IgG/IgA antibodies
4. Echovirus IgG/IgA antibodies
5. Yersinia ELISpot
6. Campylobacter IgG/IgA antibodies
7. EBV ELISpot
8. CMV ELISpot
9. Mycoplasma pneumoniae IgG/ IgA antibodies
10. Chlamydia pneumoniae IgG/ IgA antibodies

Phytobox range specifically for viral and bacterial pathogens

INGREDIENTS:

PhytoBox NO. 01

Support for Borrelia and intracellular infective pathogens

INGREDIENTS (4 CAPSULES):	DAILY DOSAGE	%RQ*
Monolaurine	900 mg	-
Baikal skullcap extract	1000 mg	-

PHYTOBOX NO. 02

Support for neuroborreliosis and neuropathic dysfunctions

INGREDIENTS (2 CAPSULES):	DAILY DOSAGE	%RQ*
Andrographis paniculata extract 4:1	400 mg	-
Uncaria rhyunchophylla	320 mg	-
Thereof Ginsenosides	256 mg	-
Polygonum cuspidatum	168,4 mg	-
Thereof trans-Resveratrol	159,8 mg	-
Grapefruit seed extract	60 mg	-
Thereof Bioflavonoids	27 mg	-

PHYTOBOX NO. 03

Break down of pleomorphic forms and support of detoxification & purification

INGREDIENTS (4 CAPSULES):	DAILY DOSAGE	%RQ*
Chlorella pyrenoides	800 mg	-
Stinging Nettle extract 10:1	160 mg	-
Bilberry extract	160 mg	-
Thereof Anthocyanidins	40 mg	-
Cranberry extract	160 mg	-
Thereof Polyphenols	40 mg	-
Lingonberry fruit powder	160 mg	-
Artichoke extract 12:1	160 mg	-
Thereof Cynarin	4 mg	-
Sage leaf extract 4:1	100 mg	-
Wild garlic herb extract 4:1	50 mg	-
Cistus incanus	50 mg	-

*RQ = Reference quantity for daily

PHYTOBOX NO. 04

Anti-inflammatory and pain relieving

INGREDIENTS (4 CAPSULES):	DAILY DOSAGE	%RQ*
OPC Grape seed extract	200 mg	-
Thereof Polyphenols	190 mg	-
Thereof OPC	100 mg	-
Curcuma Extract	200 mg	-
Thereof Curcuminoids	180 mg	-
Thereof Curcumin	140 mg	-
Rutin Powder	189,4 mg	-
Thereof Rutin	179,8 mg	-
Polygonum cuspidatu	147,4 mg	-
Thereof trans-Resveratrol	140 mg	-

PHYTOBOX NO. 05

Synbiotic with prebiotic

INGREDIENTS (4 CAPSULES):	DAILY DOSAGE	%RQ*
Acacia fibre	1.400 mg	
thereof dietary fibre	1.260 mg	
Bacterial cultures	ca. 1,2* 10^10 KBE**	
Biotin	50 µg	100
Niacin	16 mg	100
Riboflavin	1,4 mg	100

**KBE = colony forming units

PHYTOBOX NO. 06

Support in chronic opportunistic virus infection, especially herpes verdiae

INGREDIENTS (3 CAPSULES):	DAILY DOSAGE	%RQ*
Zinc	10 mg	100%
Triphala extract	600 mg	-
thereof tannins	240 mg	-
Propolis extract	120 mg	-
thereof flavonoids	17 mg	-
Lemon balm extract	100 mg	-
thereof rosmarinic acid	3 mg	-
Pomegranate extract	100 mg	-
thereof ellagic acid	40 mg	-
Thyme extract	80 mg	-
thereof essential oil	1,6 mg	-
Ginger extract	50 mg	-

PHYTOBOX NO. 07

Support in cytokine storms

INGREDIENTS (4 CAPSULES):	DAILY DOSAGE	%RQ*
Licorice root extract	880mg	-
thereof glycyrrhizin	26mg	-
Shiitake extract	650mg	-
Black cumin extract	600mg	-
Astaxanthin	4mg	-

PHYTOBOX NO. 08

Support in bartonella infection

INGREDIENTS (2 CAPSULES):	DAILY DOSAGE	%RQ*
Herba houttuyniae extract 4:1	300 mg	-
Oregano extract	90 mg	-
thereof rosamaric acid	1,8 mg	-
Fenugreek seed 8:1 extract	75 mg	-
thereof saponins	15 mg	-
Cinnamon extract 10:1	50 mg	-
Liquorice root	27 mg	-
Willow bark dry extract	25 mg	-
thereof Salicin	3,75 mg	-
Cistus incanus extract	25 mg	-
thereof polyphenols	16,25 mg	-
Grapefruit seed extract	25 mg	-
thereof flavonoids	11,25 mg	-
Cloves 4:1 extract	17 mg	-
thereof flavonoids	11,25 mg	-
Uncaria rhynchophylla 10:1 extract	4,75 mg	-
thereof indole alkaloids	0,9 mg	-
Garlic 15:1 Extract	3,5 mg	-
thereof allin	0,9 mg	-

PHYTOBOX NO. 09

Support in Chlamydia Pneumoniae infection

INGREDIENTS (3 CAPSULES):	DAILY DOSAGE	%RQ*
Vitamin C	200 mg	250
Nasturtium extract	500 mg	-
Horseradish root extract	500 mg	-
Chinese Lime Tree Extract	300 mg	-
White mustard extract	120 mg	-
of which Sinalbin	7,2 mg	-
Barberry extract	85 mg	-

PHYTOBOX NO. 10

NK Cell support

INGREDIENTS (4 CAPSULES):	DAILY DOSAGE	%RQ*
Vitamin C	40 mg	50
Reishi Extract	600 mg	-
Shiitake extract	600 mg	-
Spirulina Powder	350 mg	-
Cordyceps Extract	300 mg	-
Maitake extract	300 mg	-
Ginseng root extract	35 mg	-
thereof ginsenosides	2,8 mg	-

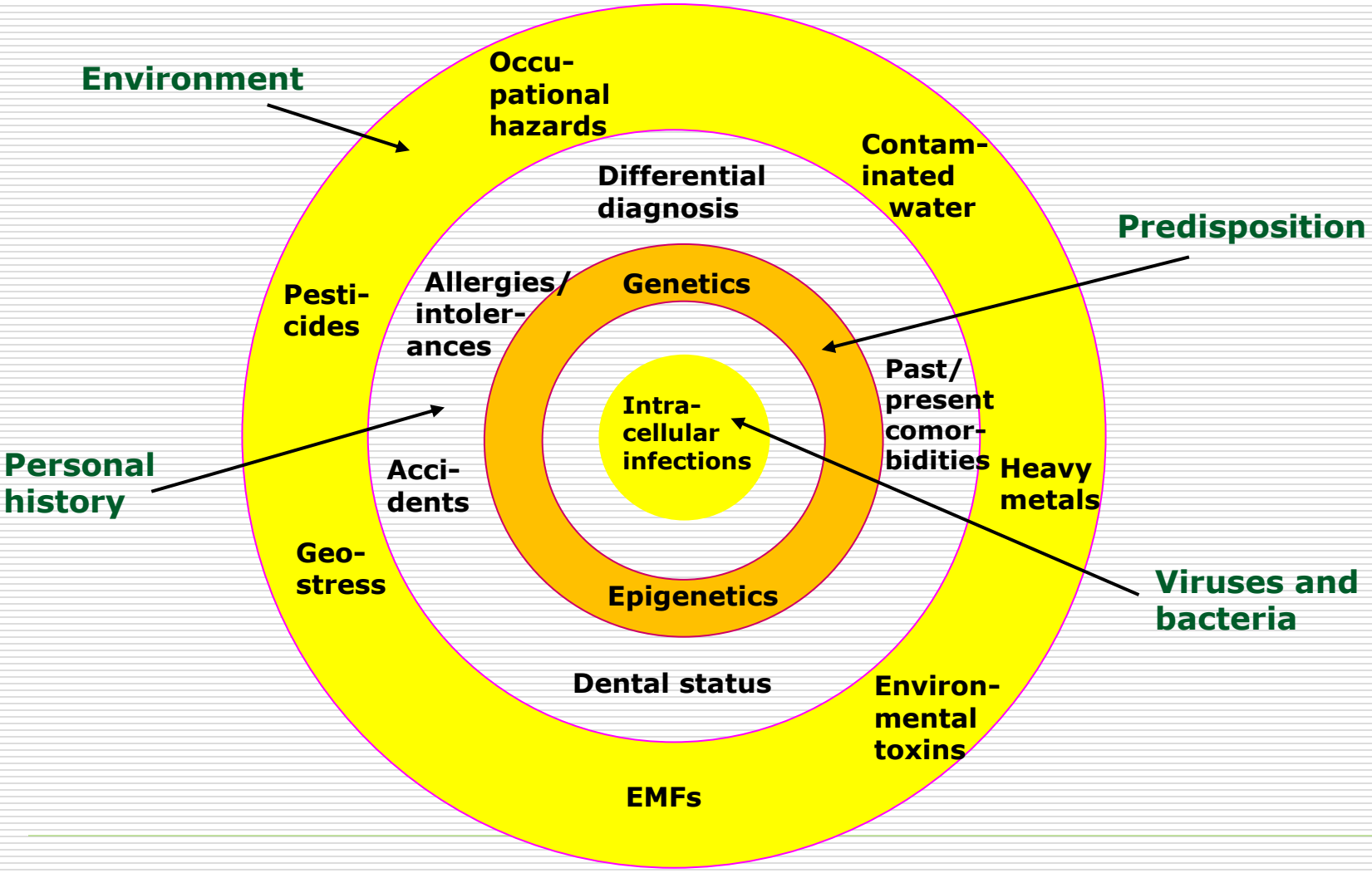
PHYTOBOX NO. 11

Support in Coxsackie and Echoviruses infection

INGREDIENTS (3 CAPSULES):	DAILY DOSAGE	%RQ*
Elderflower extract	500 mg	-
thereof Rutin	25 mg	-
Rhodiola rosea extract	250 mg	-
thereof Salidroside	7,5 mg	-
Astragalus membranaceus root extractt	250 mg	-
Oregano extract	180 mg	-
thereof Rosmarinic acid	3,6 mg	-
Barberry extract	150 mg	-
Mint, Tibetan	150 mg	-
Ginkgo biloba	80 mg	-
thereof Flavone glycoside	19 mg	-
thereof ginkgolides	4,8 mg	-
St. John's wort extract	50 mg	-
thereof Hypericin	0,15 mg	-

https://aonm.org/shop/phytobox/

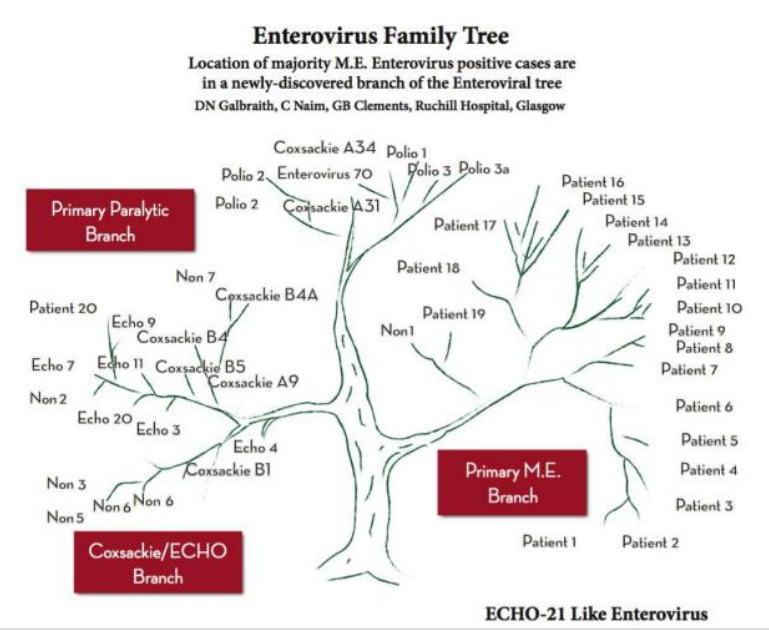
"Peeling the onion"



Enteroviruses

The Doctors and Mr. Hyde: Amy Brown's M.E Enterovirus Story
https://www.healthrising.org/blog/2017/05/23/doctors-hyde-amy-browns-m-e-enterovirus-story/

Dr. Byron Hyde has found that enteroviruses underlie most cases of M.E. that he has investigated:
https://aonm.org/wp-content/uploads/2019/05/Dr.-Byron-Hyde-MorningTalk.pdf
https://aonm.org/wp-content/uploads/2019/05/Dr.-By
https://www.youtube.com/watch?v=cx5w227VHWI



Source: http://www.microbiologybook.org/virol/picorna.htm; https://www.me-foreningen.no/wp-content/uploads/2017/05/What-is-Myalgic-Encephalom-2017-4-16.pdf

Articles on Enteroviruses

For further information on
Coxsackie A & B,see: “Coxsackie – Doing damage to our very core: the energy delivery mechanisms of our heart?” (Article 3)
https://aonm.org/wp-content/uploads/2018/10/AONM-Newsletter-October-2018-lr.pdf

For info on Enteroviruses, see “How pernicious are Enteroviruses?: Echovirus” (Article 2)
https://aonm.org/wp-content/uploads/2019/02/AONM-Newsletter-February-2019.pdf

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5857577/


frontiers in Molecular Neuroscience

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Enteroviral Infection: The Forgotten Link to Amyotrophic Lateral Sclerosis?

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