SARS-CoV-2 and viral coinfections

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Agenda

- SARS-CoV-2/COVID-19: Herpes viruses (DNA viruses)
- SARS-CoV-2/COVID-19: Enteroviruses (RNA viruses)
- Syncytia: What are they, and what are the implications?
- New Harvard study: Is EBV the leading cause of MS?
- Viral testing with Arminlabs

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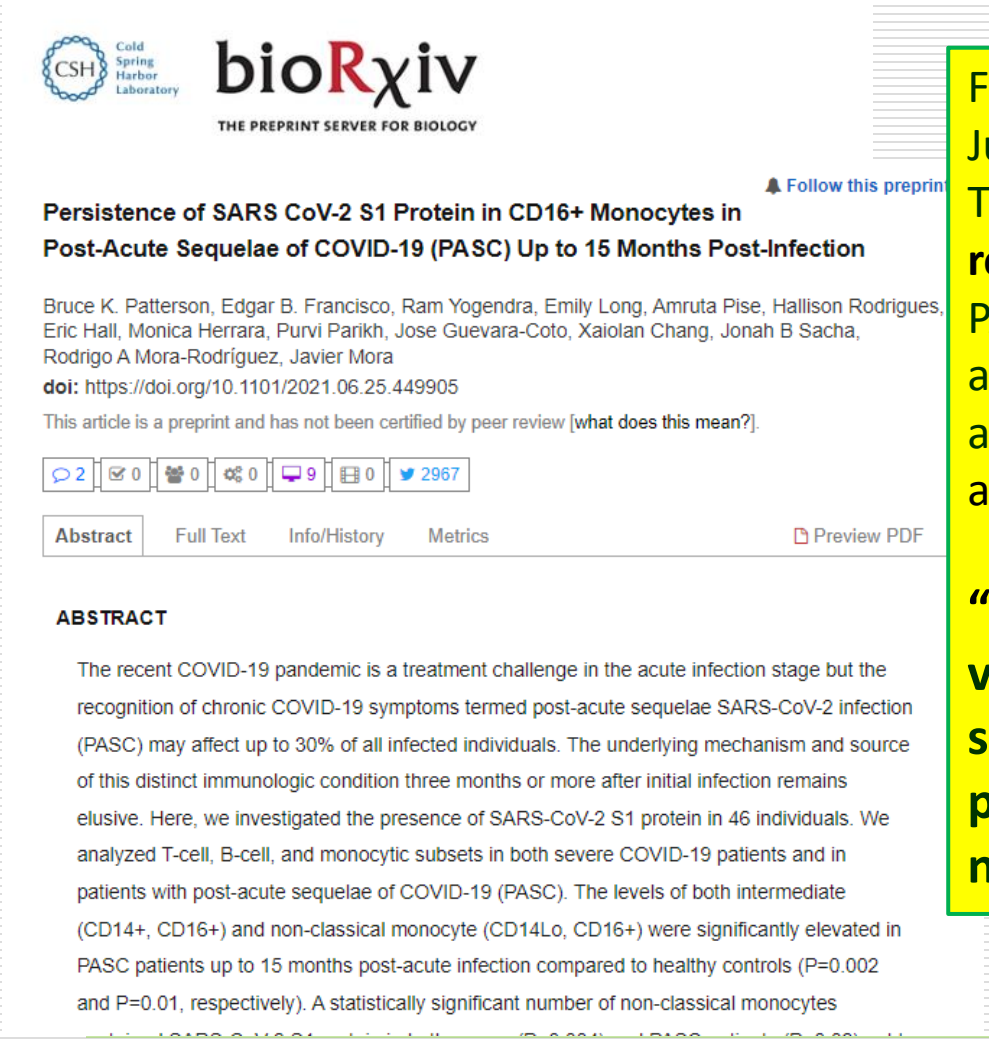
The SARS-CoV-2 Spike protein S1 segment infects monocytes that then act as a viral reservoir



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Persistence of SARS CoV-2 S1 Protein in CD16+ Monocytes in Post-Acute Sequelae of COVID-19 (PASC) Up to 15 Months Post-Infection

Bruce K. Patterson, Edgar B. Francisco, Ram Yogendra, Emily Long, Amruta Pise, Hallison Rodrigues, Eric Hall, Monica Herrara, Purvi Parikh, Jose Guevara-Coto, Xaiolan Chang, Jonah B Sacha, Rodrigo A Mora-Rodríguez, Javier Mora

doi: https://doi.org/10.1101/2021.06.25.449905

This article is a preprint and has not been certified by peer review [what does this mean?].

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ABSTRACT

The recent COVID-19 pandemic is a treatment challenge in the acute infection stage but the recognition of chronic COVID-19 symptoms termed post-acute sequelae SARS-CoV-2 infection (PASC) may affect up to 30% of all infected individuals. The underlying mechanism and source of this distinct immunologic condition three months or more after initial infection remains elusive. Here, we investigated the presence of SARS-CoV-2 S1 protein in 46 individuals. We analyzed T-cell, B-cell, and monocytic subsets in both severe COVID-19 patients and in patients with post-acute sequelae of COVID-19 (PASC). The levels of both intermediate (CD14+, CD16+) and non-classical monocyte (CD14Lo, CD16+) were significantly elevated in PASC patients up to 15 months post-acute infection compared to healthy controls (P=0.002 and P=0.01, respectively). A statistically significant number of non-classical monocytes

From the seminal Bruce Patterson article June 2021:
The S1 segment of the spike protein is **recoverable from human monocytes** in PASC patients **up to 15 months** after their acute infection, compared to controls, and it appears that these monocytes are able to act as a **viral reservoir:**

"The significance of these cells as a viral protein reservoir in PASC is supported by our data reporting the presence of S1 protein within nonclassical monocytes."

Source: *https://www.biorxiv.org/content/10.1101/2021.06.25.449905v1*

"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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[2] Department of Public Health, Kahramanmaraş Sütçü İmam University, Kahramanmaraş 46040, Turkey; razim01@gmail.com
[3] Warren Alpert Medical School of Brown University, Providence, RI 02903, USA; warren.licht@brownphysicians.org
[4] College of Veterinary Medicine, University of Georgia, Athens, GA 30602, USA; djhurley@uga.edu
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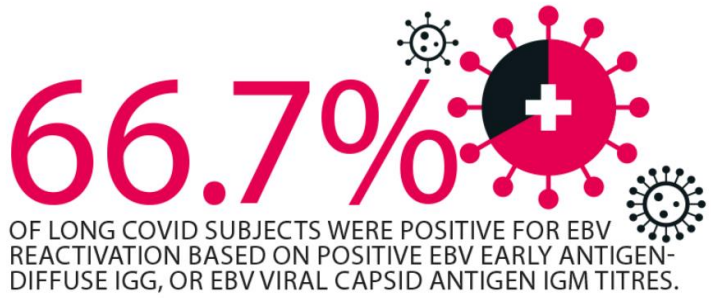
Abstract: Coronavirus disease 2019 (COVID-19) patients sometimes experience long-term symptoms following resolution of acute disease, including fatigue, brain fog, and rashes. Collectively these have become known as long COVID. Our aim was to first determine long COVID prevalence in 185 randomly surveyed 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]

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

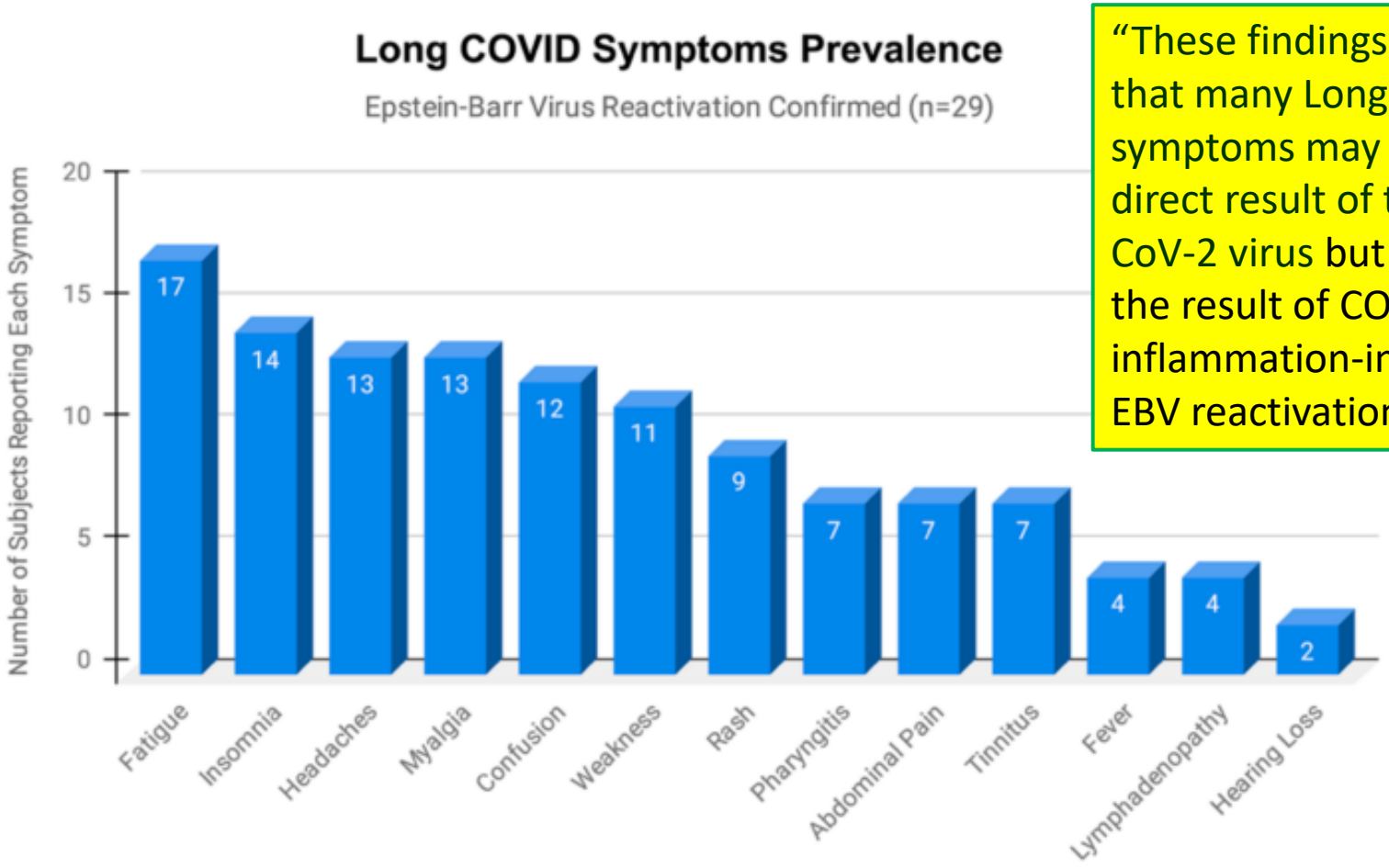
ABSTRACT Understanding factors that affect the infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is central to combatting coronavirus disease 2019 (COVID-19). The virus surface spike protein of SARS-CoV-2 mediates viral entry into cells by binding to the ACE2 receptor on epithelial 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/*

Long COVID symptoms correlate with EBV reactivation – statistically very significant



"These findings suggest that many Long-COVID symptoms may not be a direct result of the SARS-CoV-2 virus but may be the result of COVID-19 inflammation-induced EBV reactivation."

Source: *https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8233978/*

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

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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.

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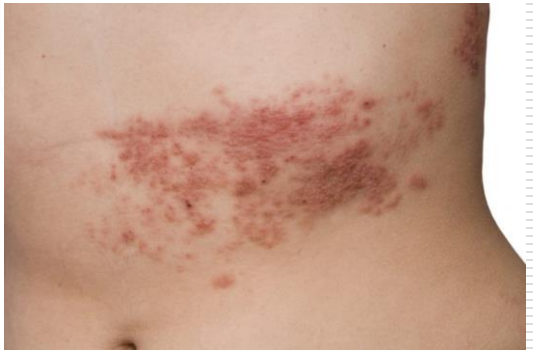
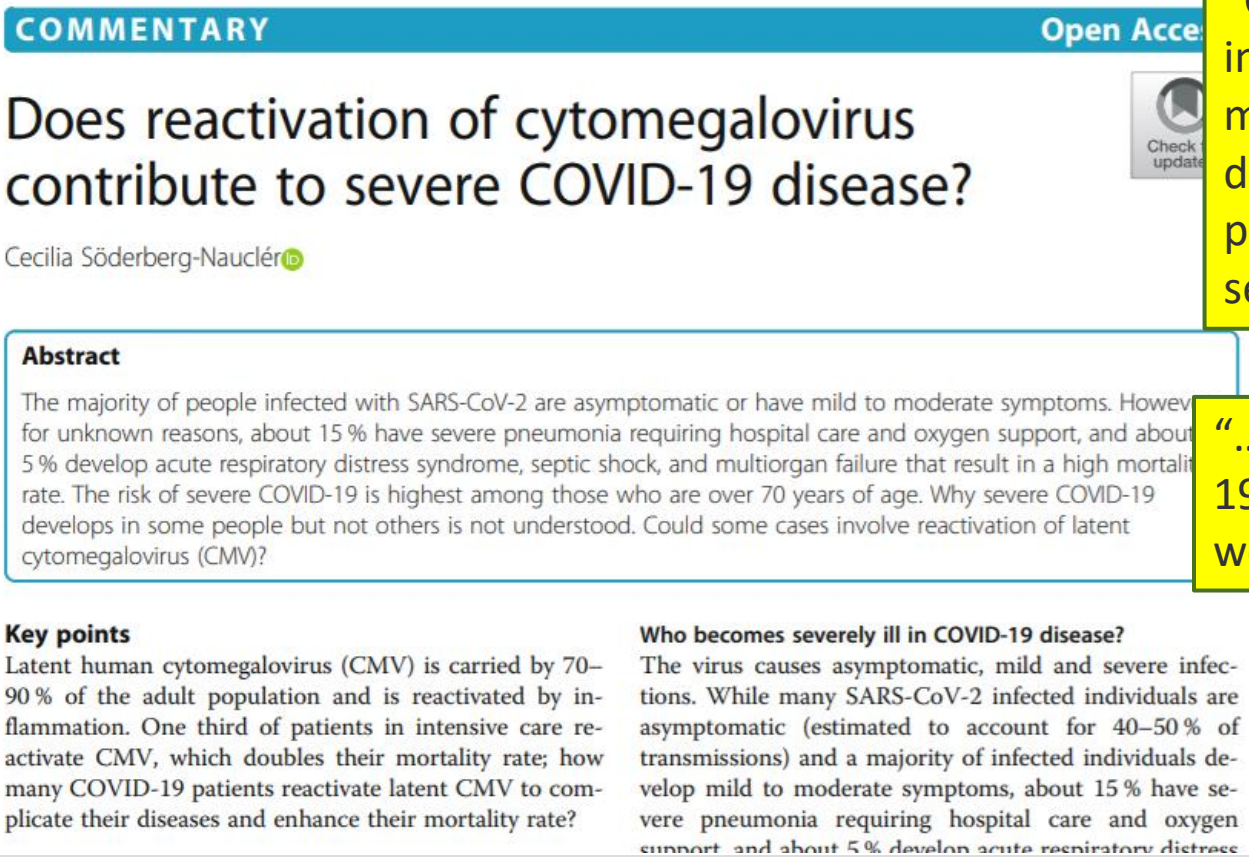
NPub.org/COVID19

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,*]

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.

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

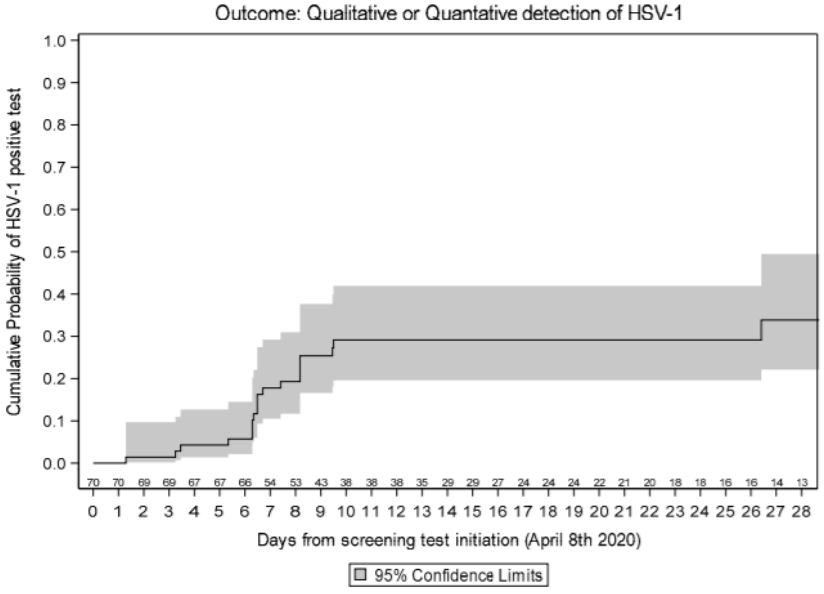


Figure 1. Kaplan–Meier estimates of HSV re-activation.

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

Association of HHV-6, too

JOURNAL OF
MEDICAL VIROLOGY

SHORT COMMUNICATION | Free Access

Presence and clinical impact of human herpesvirus-6 infection in patients with moderate to critical coronavirus disease-19

Katia Lino, Lilian S. Alves, Jessica V. Raposo, Thalia Medeiros, Cintia F. Souza, Andrea A. da Silva, Vanessa S. de Paula, Jorge R. Almeida

First published: 14 October 2021 | https://doi.org/10.1002/jmv.27392

4 DISCUSSION

As a pilot study, we investigated the active infection of HHV-6 using nasopharyngeal samples from patients infected with SARS-CoV-2 with moderate to critically ill hospitalized, we found an impressive frequency of 21.7% of HHV-6. A recent study performed in blood samples found 22% of HHV-6 infection among COVID-19 patients in an intensive care unit.[19] All 13 positive cases of HHV-6 were identified as HHV-6B species.

In addition, our aim was also to assess the role of some clinical risk comorbidities and in-hospital outcomes, including mortality, and we were able to demonstrate a significant relationship only with prior therapeutic immunosuppression (as we can see in SLE and kidney transplant patients, for example). Besides, trying to create some relation with cutaneous or neurological manifestations, we realized that this information was very poorly described in medical records and we discuss this.

A very important issue is that herpesvirus reactivation has been reported to be very common in critically ill patients even before the COVID-19 pandemic,[19-21] as well as in cancer, autoimmune diseases, and organ transplantation.[1, 22] Guidelines exist in this setting

"As a pilot study, we investigated the active infection of HHV-6 using nasopharyngeal samples from patients infected with SARS-CoV-2 with moderate to critically ill hospitalized, we found an impressive frequency of 21.7% of HHV-6. A recent study performed in blood samples found 22% of HHV-6 infection among COVID-19 patients in an intensive care unit."

Source: https://onlinelibrary.wiley.com/doi/10.1002/jmv.27392

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Coxsackie and myocarditis/pericarditis in coinfections with COVID-19

Fulminant myocarditis as an early presentation of SARS-CoV-2

Tamara Naneishvili,[✉1] Arsalan Khalil,[1] Ryan O'Leary,[2] and Neeraj Prasad[1]

Abstract

Myocarditis is well known to be caused by viral infections s
herpes virus 6 and parvovirus B19. However, during the current emerging outbreak of SARS-CoV-2, there have been few case reports describing myocarditis as a possible presentation. In our case re-

"**Myocarditis** is well known to be caused by viral infections such as **Coxsackie virus group B**, human herpes virus 6 and parvovirus B19."[1]

"Both types of **[Coxsackie]**viruses (A and B) can cause meningitis, myocarditis, and pericarditis"[2]

Journal List > Elsevier Public Health Emergency Collection > PMC8503119

Elsevier Public Health Emergency Collection
Public Health Emergency COVID-19 Initiative

Chest. 2021 Oct; 160(4): A976. PMCID: PMC8503119
Published online 2021 Oct 11. doi: 10.1016/j.chest.2021.07.909

COVID-19 AND COXSACKIE B COINFECTION: A RARE CASE OF ACUTE PERICARDITIS

AMANDA ENG, NIKISHA PANDYA, and RATTAN PATEL

… this is the first case presenting **pericarditis caused by COVID 19 and Coxsackieviruses B (CV-B) coinfection**.

Source: 1. https://pubmed.ncbi.nlm.nih.gov/32928810/; 2. https://www.medicinenet.com/coxsackie_virus/article.htm; https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC8503119/; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8330013/pdf/IETT_0_1952985.pdf

Possible association of Coxsackie with SARS-CoV-2 in oral cavity lesions

frontiers in Medicine

REVIEW
published: 14 January 2021
doi: 10.3389/fmed.2020.571214

Association of Viral Infections With Oral Cavity Lesions: Role of SARS-CoV-2 Infection

Giusy Rita Maria La Rosa[1]*, *Massimo Libra*[2], *Rocco De Pasquale*[1], *Sebastiano Ferlito*[1] and *Eugenio Pedullà*[1]

[1] Department of General Surgery and Medical-Surgical Specialties, University of Catania, Catania, Italy, [2] Department of Biomedical and Biotechnological Sciences, Oncologic, Clinic and General Pathology Section, University of Catania, Catania, Italy

Different viral agents, such as herpesviruses, human papillomavirus, and Coxsackie virus, are responsible for primary oral lesions, while other viruses, such as human immunodeficiency virus, affect the oral cavity due to immune system weakness. Interestingly, it has been reported that coronavirus disease 2019 (COVID-19) patients can show cutaneous manifestations, including the oral cavity. However, the association between oral injuries and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is still unclear. This narrative review aimed to summarize the available literature and provide an overview of oral lesions associated with COVID-19. An online literature search was conducted to select relevant studies published up to November 2020.

OPEN ACCESS

Edited by:
Chaminda Jayampath Seneviratne,

"Different viral agents, such as herpesviruses, human papillomavirus, and Coxsackie virus, are responsible for primary oral lesions, while other viruses, such as human immunodeficiency virus, affect the oral cavity due to immune system weakness. Interestingly, it has been reported that coronavirus disease 2019 (COVID-19) patients can show cutaneous manifestations, including the oral cavity."

Source: https://www.ncbi.nlm.nih.gov/labs/pmc/articles/PMC7840611/

Multiple viruses associated with oral lesions: SARS-CoV-2 may eventually need adding to the list

TABLE 1 | Viruses associated with oral lesions.

Viral family	Virus	Oral disease	Oral lesion
Herpesvirus (HSV)	HSV-1	Primary herpetic gingivostomatitis Herpes labialis (recurrent infection)	Vesicles Erosions Ulcers
	HSV-2	Similar to HSV-1 but rare	
	HSV-3 (Varicella zoster)	Primary infection (rare) Recurrent infection	
	HSV-4 (Epstein Barr)	Mononucleosis Burkitt's lymphoma Nasopharyngeal carcinoma	
	HSV-5 (Citomegalovirus)	Sialadenopathy Aphthae	
	HSV-6	-	
	HSV-7	-	
	HSV-8	Kaposi's sarcoma	
Papillomavirus (HPV)	More than 100 subtypes: HPV-2,−6,−11,−57	Squamous papillomas Verruca vulgaris	Exophytic papillary lesions Multiple, pink, soft tissue masses
	HPV-6 and−11	Condyloma acuminatum	
	HPV-13 and−32	Focal epithelial hyperplasia (Heck's disease)	
	HPV-16 and−18	Dysplastic and neoplastic transformations of squamous epithelium	
Poxvirus	Variola Molluscum contagiosum (MCV)	Smallpox Molluscum contagiosum	Maculopapular lesions Erythematous papules
Picornavirus	Coxsackie virus: A16, A6 A1-A6, A8, A10, A22	Hand, foot, and mouth disease Herpangina	Vesicles Ulcers
Paramyxovirus	Measles virus (MV) Mumps virus	Rubeola Mumps	Small erythematous macules with white necrotic center (Koplik's spots) Ulcers
Retrovirus	Human immunodeficiency virus (HIV)	Opportunistic infections (viral, bacterial, fungal) Malignancies	Not typical lesions but dependent on the secondary lesion

Source: https://pubmed.ncbi.nlm.nih.gov/33521007

Coxsackie frequently found in ME – especially B1

"L. … myalgic encephalomyelitis (ME) .. occurs as both sporadic and epidemic cases. It is a poorly characterized illness, the cardinal feature being excess fatiguability of the skeletal muscles. Other symptoms that may be present include muscle pain, headache, inability to concentrate, paraesthesiae, impairment of short term memory and poor visual accommodation. Focal neurological signs are rare. Evidence of myopericarditis may be present occasionally. There may be a history of a nonspecific viral illness and some lymphadenopathy may be present. Routine laboratory investigations are usually normal. Recovery usually takes place within a few weeks or months but the illness may persists in some patients with periods of remission and relapse.

The aetiology is uncertain but it is thought that there is a substantial functional component as well as a viral component in many cases. ME occasionally follows confirmed virus infections such as varicella/zoster, influenza A and IM. It may follow some bacterial infections such as toxoplasma gondii and leptospira. In the majority of cases though, the initiating infection cannot be diagnosed specifically. **There is now substantial evidence for a persistent enterovirus infection, particularly coxsackie B viruses in many cases of ME. Patients with ME appears to have a higher prevalence of antibodies against coxsackie B viruses than matched controls. Furthermore, coxsackie B viruses may occasionally be isolated from the faeces as well as skeletal muscle biopsies in patients with ME."**

Source: http://virology-online.com/viruses/Enteroviruses5.htm

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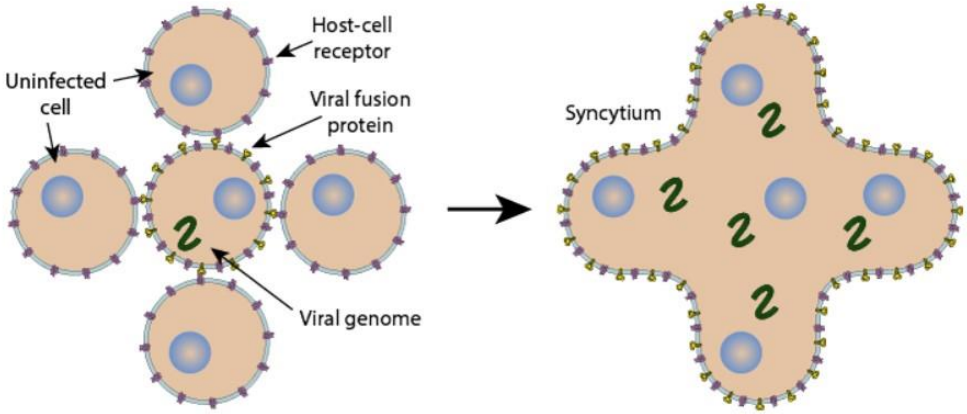
The tendency of SARS-CoV-2 to form multinucleate cells is shared by other viruses, too

E



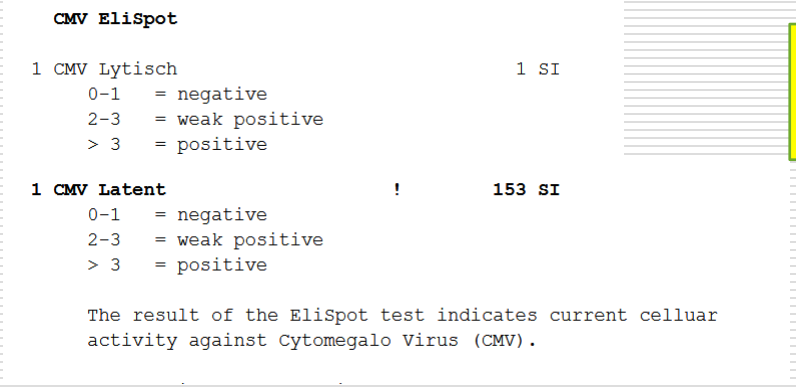
A March 2021 article in iScience entitled "*Quantitative assays reveal cell fusion at minimal levels of SARS-CoV-2 spike protein and fusion from without*" highlights the fusogenic activity of the S protein of the SARS-CoV-2 virus: it is not just a passive anchor – **it is biologically active, and can stick cells together**.

Syncytium formation,
https://viralzone.expasy.org/5957?outline=all_by_species

Source: https://www.sciencedirect.com/science/article/pii/S2589004221001383?via%3Dihub

Syncytia formation and herpes viruses

Can other viruses instigate these syncytia, too? They most definitely can: the phenomenon is well-known for example in many of the (DNA) herpes viruses.. With the human simplex virus (HSV),(1) these syncytia have been detected in the skin. There are also studies on their development in certain types of Epstein-Barr virus(2) and Varicella Zoster virus (3).. Large syncytia have been found after infection with Cytomegalovirus ("megalo" meaning large – – perhaps a clue), and with HHV-6, too: "These findings suggest that FFWO, which HHV-6A induced in a variety of cell lines, may play an important role in the pathogenesis of HHV-6A, not only in lymphocytes but also in various tissues".(4) This would appear to be a characteristic shared particularly by the neurotropic α-herpesviruses."5



CMV EliSpot

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

1 CMV Latent ! 153 SI
0-1 = negative
2-3 = weak positive
> 3 = positive

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

The "latent" result of EBV and CMV Elispots also suggests the ability to form syncytia

Source: 1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869023/; 2. https://pubmed.ncbi.nlm.nih.gov/6273915/; 3. https://jvi.asm.org/content/78/6/2884; 4. https://jvi.asm.org/content/76/13/6750; 5 https://aonm.org/wp-content/uploads/2021/04/AONM-Newsletter-April-2021.pdf

High co-infection rate with COVID-19

CIDRAP Center for Infectious Disease Research and Policy

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FEATURED NEWS TOPICS COVID-19 Flu Vaccines Roadmap MERS-CoV Chronic Wasting Disease

Researchers report 21% COVID-19 co-infection rate

Filed Under: COVID-19

Mary Van Beusekom | News Writer | CIDRAP News | Apr 16, 2020 Share Tweet LinkedIn Email Print & PDF

A research letter published yesterday in *JAMA* found that rates of COVID-19 co-infections with other respiratory pathogens are 21%, higher than previously thought, suggesting that identification of another pathogen may not rule out the presence of the novel coronavirus.

Also, a letter yesterday in the *Annals of Internal Medicine* detailing survey results on 272 primary care physicians in Lombardy, Italy, who cared for about 400,000 COVID-19 patients found that 40% had symptoms suggestive of the disease, and most had to buy their own personal protective equipment (PPE) and educate themselves on coronavirus management.

Mohammed Haneefa Nizamudeen / iStock

Co-infection rate higher than thought

Early in the pandemic, reports from China indicated that co-infection of COVID-19 and other respiratory pathogens was uncommon, suggesting that patients who tested positive for other pathogens could be assumed to not have the novel coronavirus.

Some sites tested the specimens for COVID-19 as well as influenza A and B, respiratory syncytial virus (RSV), non–COVID-19 coronaviruses, adenovirus, parainfluenza 1 through 4, human metapneumovirus, rhinovirus/enterovirus, *Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*

Source: https://www.cidrap.umn.edu/news-perspective/2020/04/researchers-report-21-covid-19-co-infection-rate; https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30494-8/fulltext

Agenda

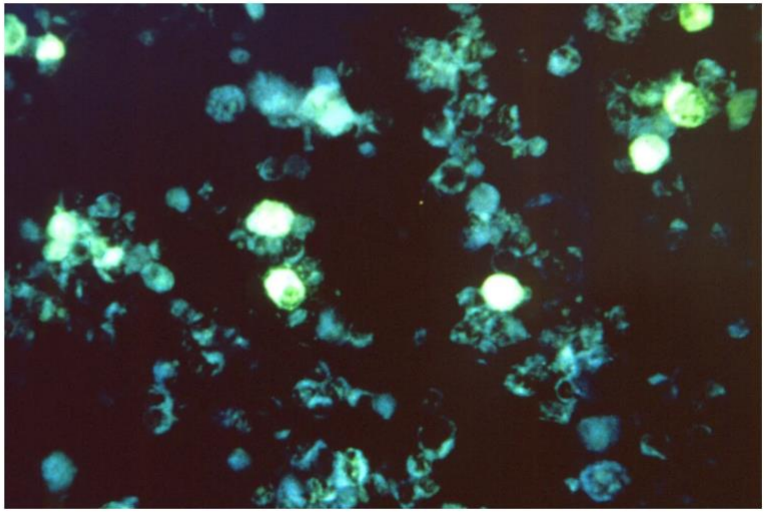
- SARS-CoV-2/COVID-19: Herpes viruses (DNA viruses)
- SARS-CoV-2/COVID-19: Enteroviruses (RNA viruses)
- Syncytia: What are they, and what are the implications?
- **New Harvard study: Is EBV the leading cause of MS?**
- Viral testing with Arminlabs

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.

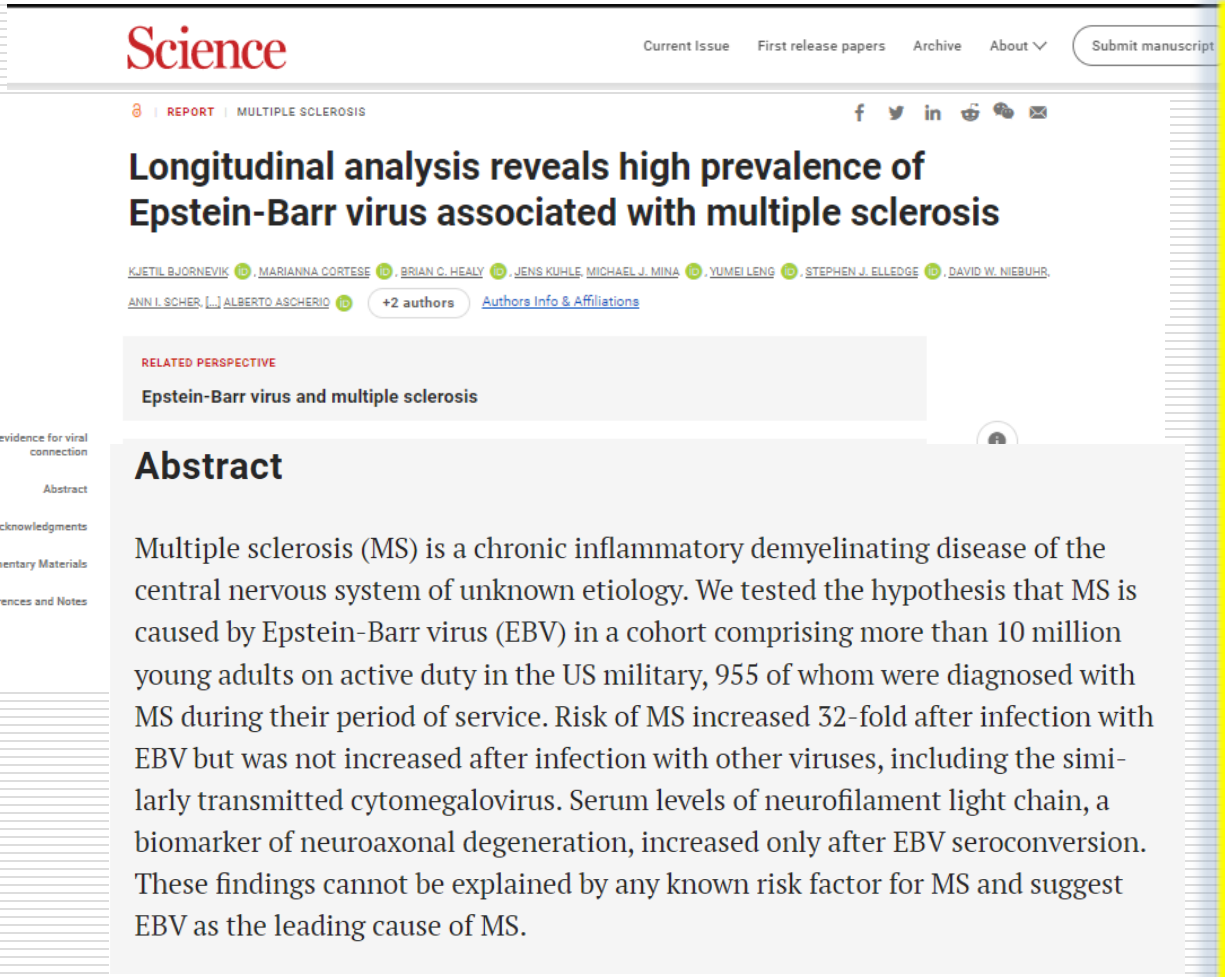
CDC

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

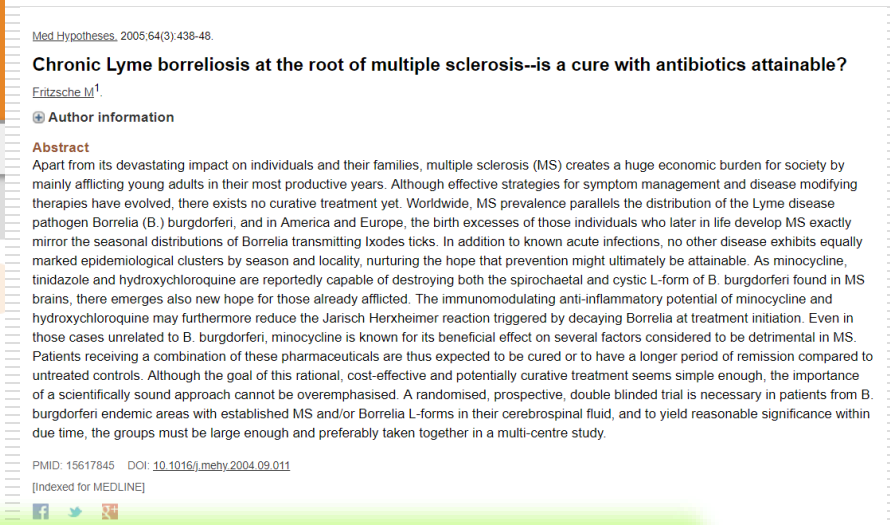
Abstract

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

Associations known with Borrelia, Bartonella and Coxsackie …. first time the EBV connection has been so strong



Dr. Vincent Marshall's exhaustive research from the 80's showed spirochetes on the axons of nerves of MS patient autopsies in Europe.

Source: https://www.ncbi.nlm.nih.gov/pubmed/15617845; http://www.medical-hypotheses.com/article/0306-9877(88)90023-0/abstract

Agenda

- SARS-CoV-2/COVID-19: Herpes viruses (DNA viruses)
- SARS-CoV-2/COVID-19: Enteroviruses (RNA viruses)
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- New Harvard study: Is EBV the leading cause of MS?
- **Viral testing with Arminlabs**

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

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

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/

Highly sensitive antibody tests also 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/

Examples of Enterovirus results

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?).

Example of our tailored testing protocols: Multiple Sclerosis (compare with checklist findings)

1. Borrelia EliSpot, Tickplex Basic
2. Chlamydia pneumoniae EliSpot, and Chlamydia pneumonia IgG/IgA antibodies
3. Mycoplasma pneumoniae Elispot, and IgG/IgA antibodies
4. Bartonella Elispot
5. Coxsackie Virus IgG/IgA antibodies
6. EBV EliSpot
7. CMV EliSpot
8. HHV6 EliSpot

Electronic checklist helps decide which infections to test for; fills automatically

Coinfections-Checklist

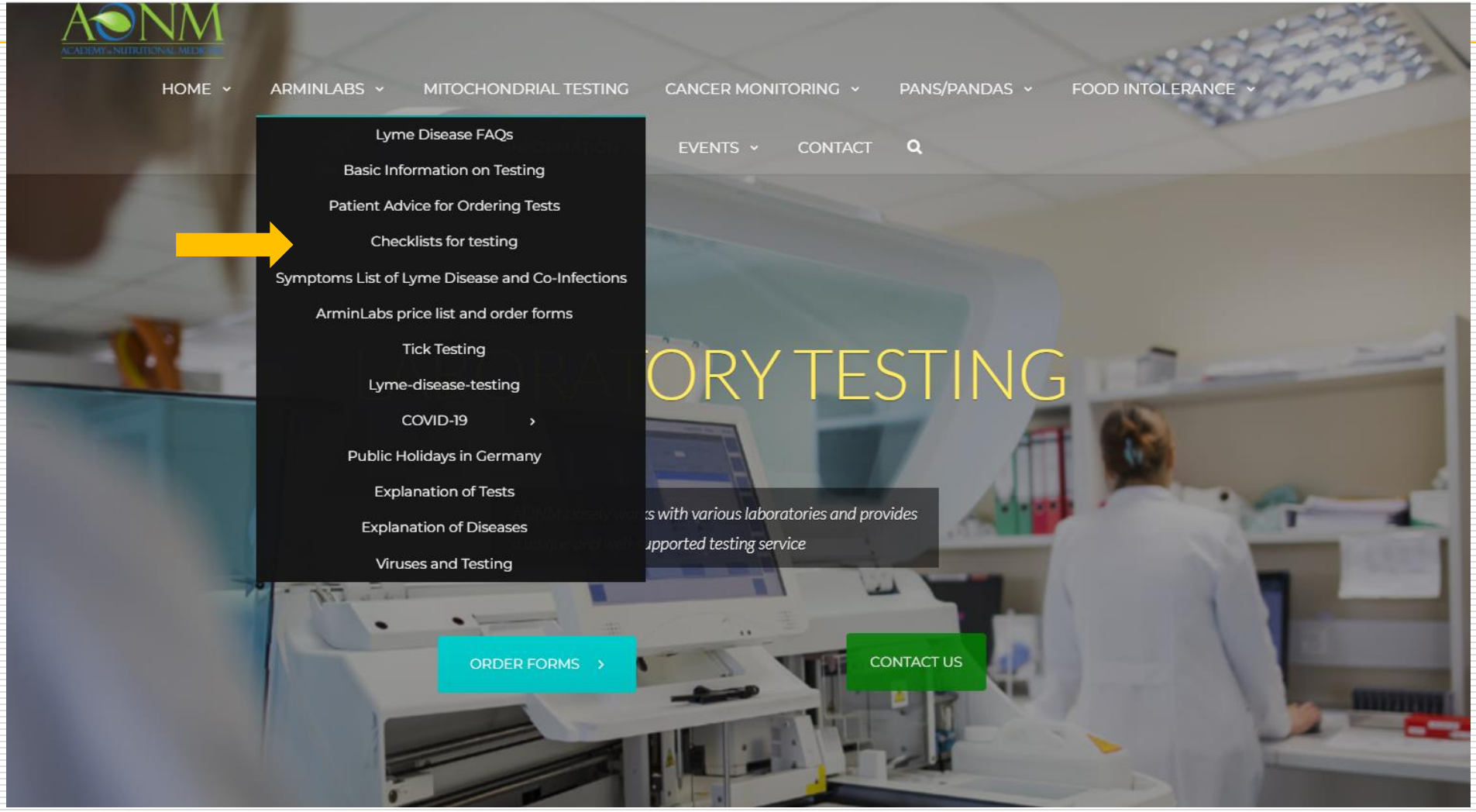
Name, first name ..... Date (DD/MM/YYYY) .....

	Actual and former symptoms Please mark with a cross	X	Score-Points (filled in by physician/naturopath)	Ranking
1	Stomach ache, gut problems	☒	Ehrlichia&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	☐		

Ranked in order of priority – Enteroviruses and Herpesviruses draw for first place here

Where to find the checklist:

www.aonm.org – ArminLabs tab



Long COVID Day on March 25th: lots of therapeutic options; both in person and online

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NUTRITIONAL AND ENVIRONMENTAL MEDICINE
LONDON ENGLAND www.biolab.co.uk

LONG COVID DAY

Long COVID Day

by Biolab Limited
18 followers Follow

£79 - £115

Tickets

A Biolab workshop for practitioners, providing a better understanding of Long COVID and sharing experiences of treatment strategies.

About this event

LONG COVID DAY

Listen to our practitioners talking about how they help their Long COVID patients

PRESENTED BY:

Dr Damien Downing	Dr Sarah Myhill
Dr Shideh Pouria	Dr Siegfried Trefzer
Dr Yassine Bendiabdalla	Professor Robert Thomas
Gilian Crowther Dip ND/NT	Mark Adams MSc
Rachel Nicoll PhD	

FRIDAY 25 MARCH 2022

On Zoom and, subject to government regulations, in person at the Holiday Inn Bloomsbury, Coram St, London WC1N 1HT

6 hours CPD applied for

Date and time

Fri, 25 March 2022
09:00 - 17:00 GMT
Add to calendar

Location

Holiday Inn London - Bloomsbury Hotel
Coram Street
London
WC1N 1HT
View Map

Refund policy

Refunds up to **7 days** before even
Eventbrite's fee is nonrefundable

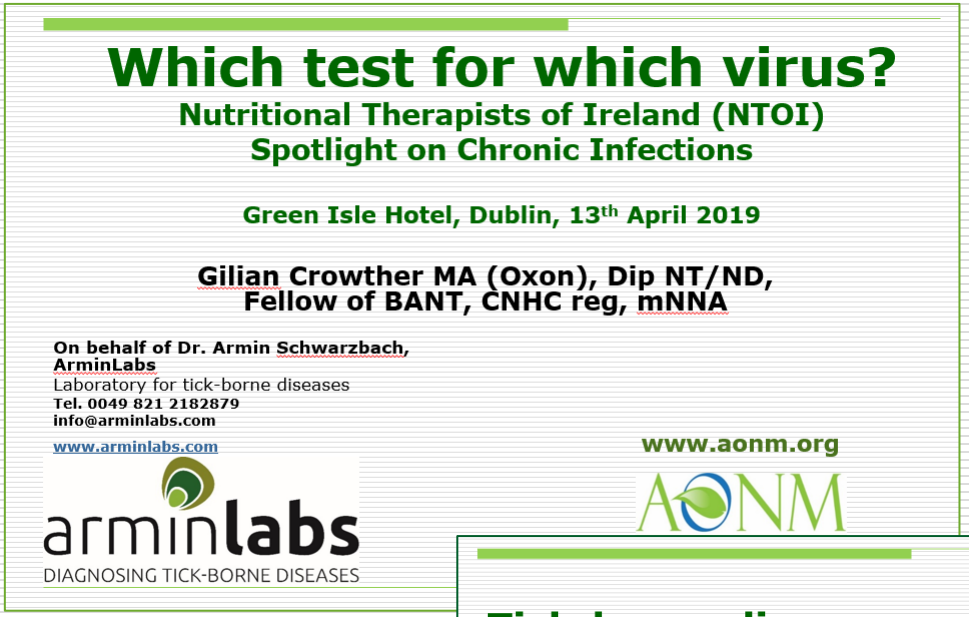
LONG COVID DAY PROGRAMME

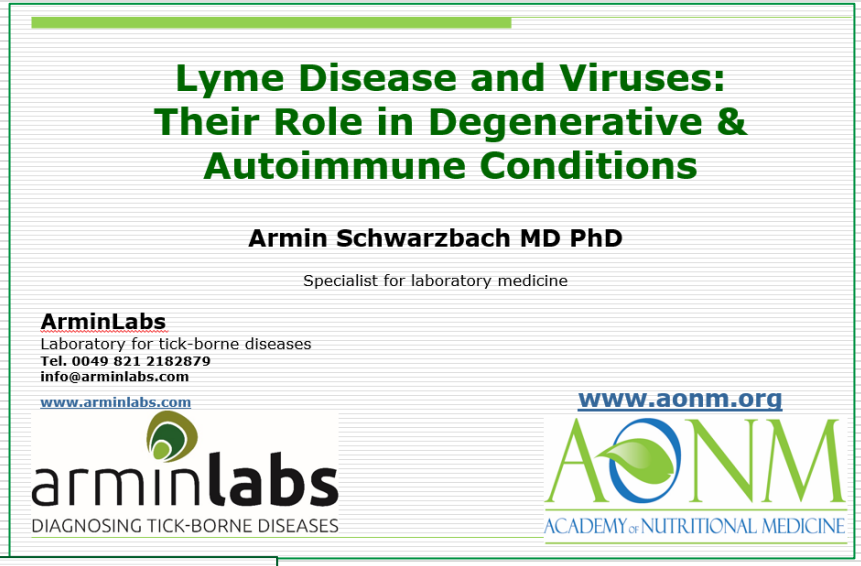
0900-0910	Mark Howard	Welcoming remarks
0910-0940	Rachel Nicoll	Introduction to Long COVID
0940-1010	Dr Siegfried Trefzer	What makes Long Covid unique
1010-1040	Dr Shideh Pouria	Modifiable risk factors in cases of Long COVID
1040-1100	Coffee/tea	
1100-1130	Dr Yassine Bendiabdallah	Systemic approaches in the management of Long Covid
1130-1200	Rachel Nicoll	Long COVID: the science Part 1
1200-1230	Dr Sarah Myhill	Management of depleted energy in Long COVID
1230-1300	Practitioner Panel	Questions
1300-1400	Lunch (not provided)	
1400-1430	Professor Robert Thomas	Results of a nutritional intervention study for Long COVID
1430-1500	Gilian Crowther	Restoring cellular homeostasis: therapeutic strategies for Long COVID
1500-1530	Rachel Nicoll	Long COVID: the science Part II
1530-1600	Coffee/tea	
1600-1630	Mark Adams	Laboratory investigations for patients with Long COVID
1630-1700	Dr Damien Downing	Treating long Covid; What we know and what we believe
1700-1730	Practitioner Panel	Questions
1730	Mark Howard	Closing remarks

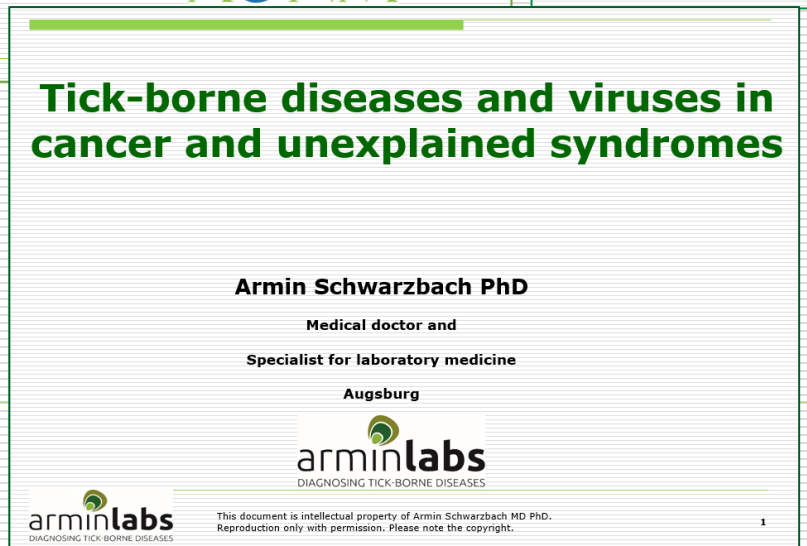
Earlybird extended to 03/03/22

Links to more detailed Arminlabs virus presentations on the AONM website …

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







… and webinars on testing for SARS-CoV-2/COVID-19

https://aonm.org/view-past-webinars/

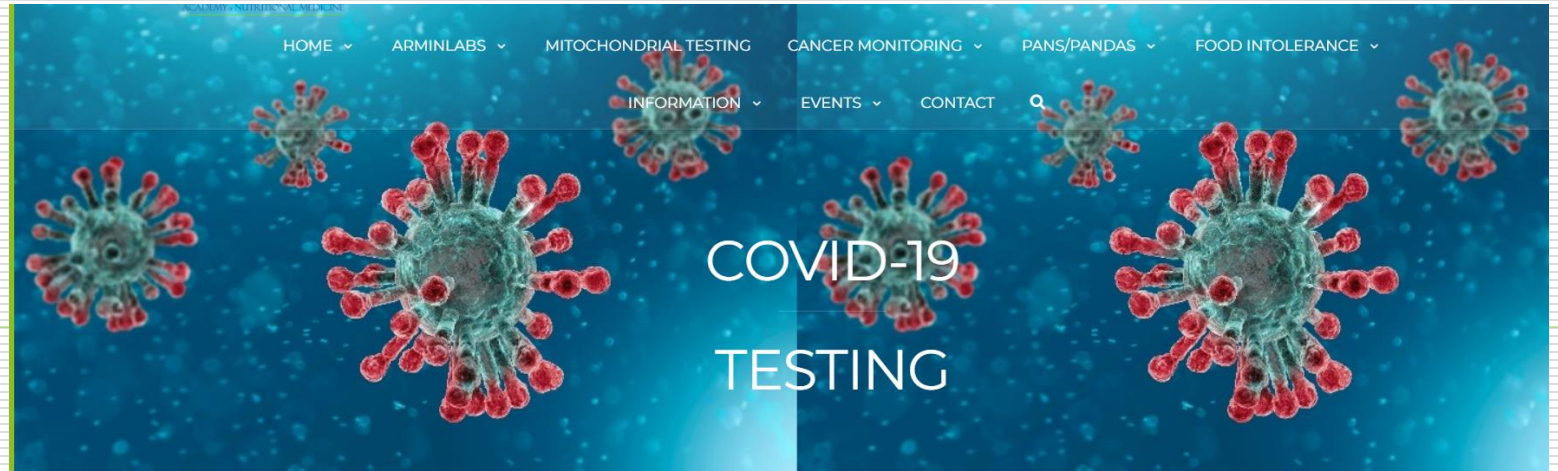
DR. ARMIN SCHWARZBACH

DR. ARMIN SCHWARZBACH ON HIS RESEARCH AND APPROACH TO COVID-19 TESTING

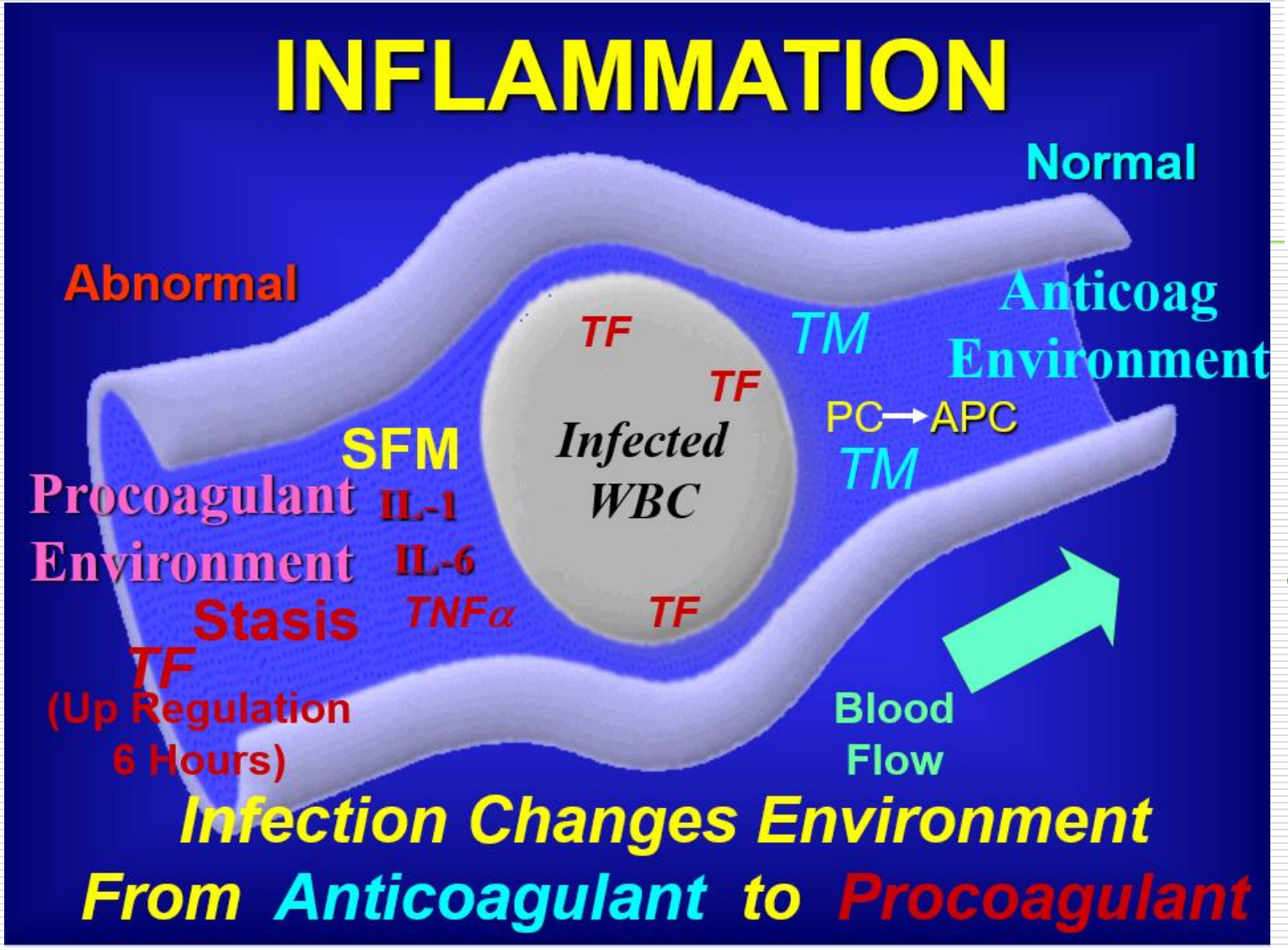
DR. ARMIN SCHWARZBACH

SARS-COV-2 TESTING PART 2

Details on T-Cell testing and antibody testing for SARS-CoV-2/ COVID-19 can be found here: https://aonm.org/covid-19/



Talk on infections and hypercoagulation (see Past webinars, Feb. 2020) also very relevant to SARS-CoV-2



Hypoxia: 1 micron of fibrin = O2 diffusion time of 5.3 mins instead of 2 seconds

Source: David Berg Coagulation 202 Proteins and Coagulation Pathways, from The Role of Hypercoagulation and Biofilms in Chronic Illness Conference (2011)

Thank you very much!
Q&A/Discussion

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