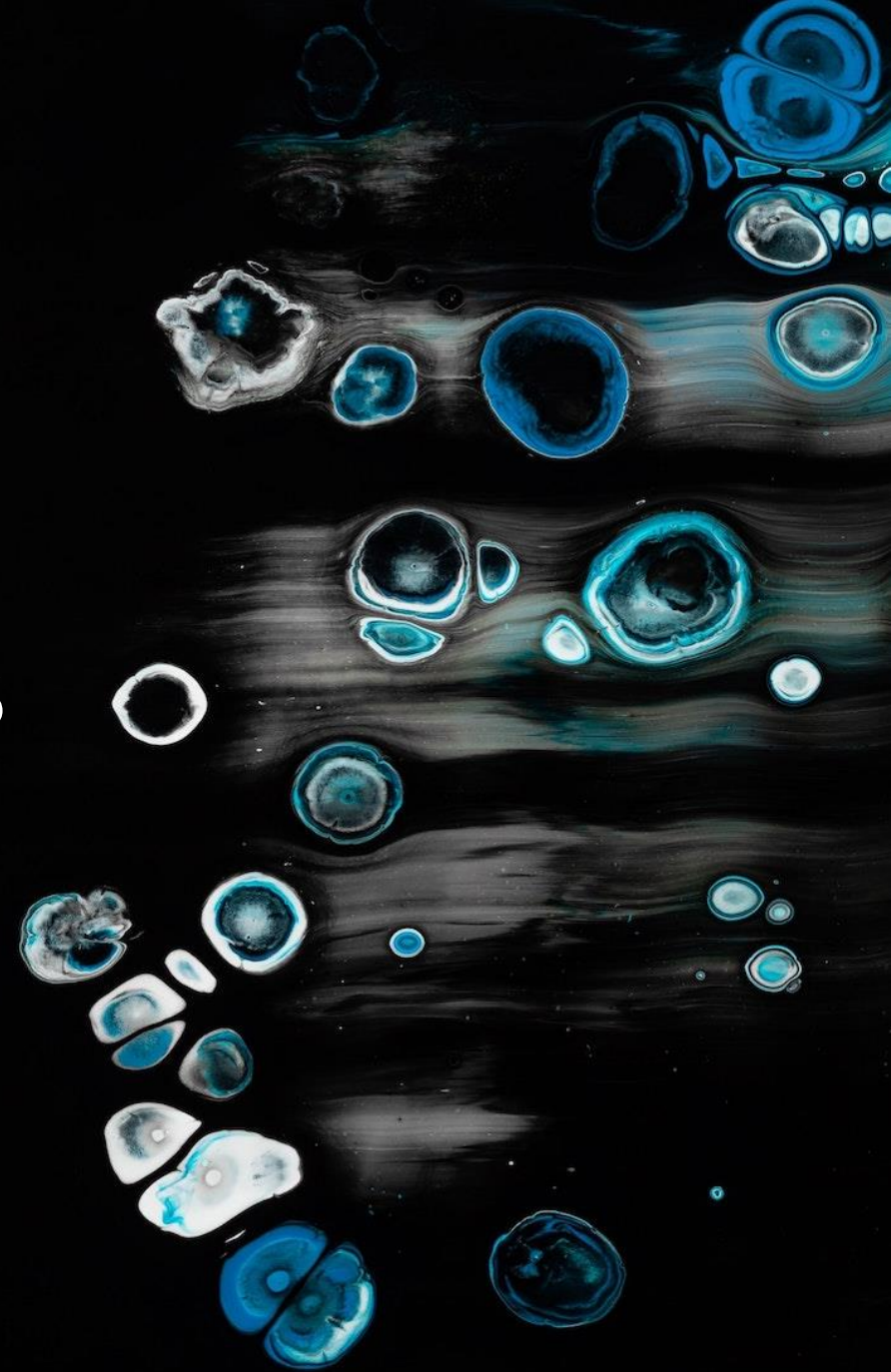




Australian
Chronic Infectious &
Inflammatory Disease
Society

HD Talk - ACIIDS re: Treatment of Infections

Dr Hugh Derham



Mast Cells as a Common Pathway to Inflammation

Mast cells can become overactive when disturbed by chemicals/toxins, or microbes, either bacterial (e.g. *Borrelia*, *Bartonella*, Strep, Staph, *E coli*, LPS) or viral (SARS-CoV-2, coxsackie, Dengue, HIV, several Hepatises).

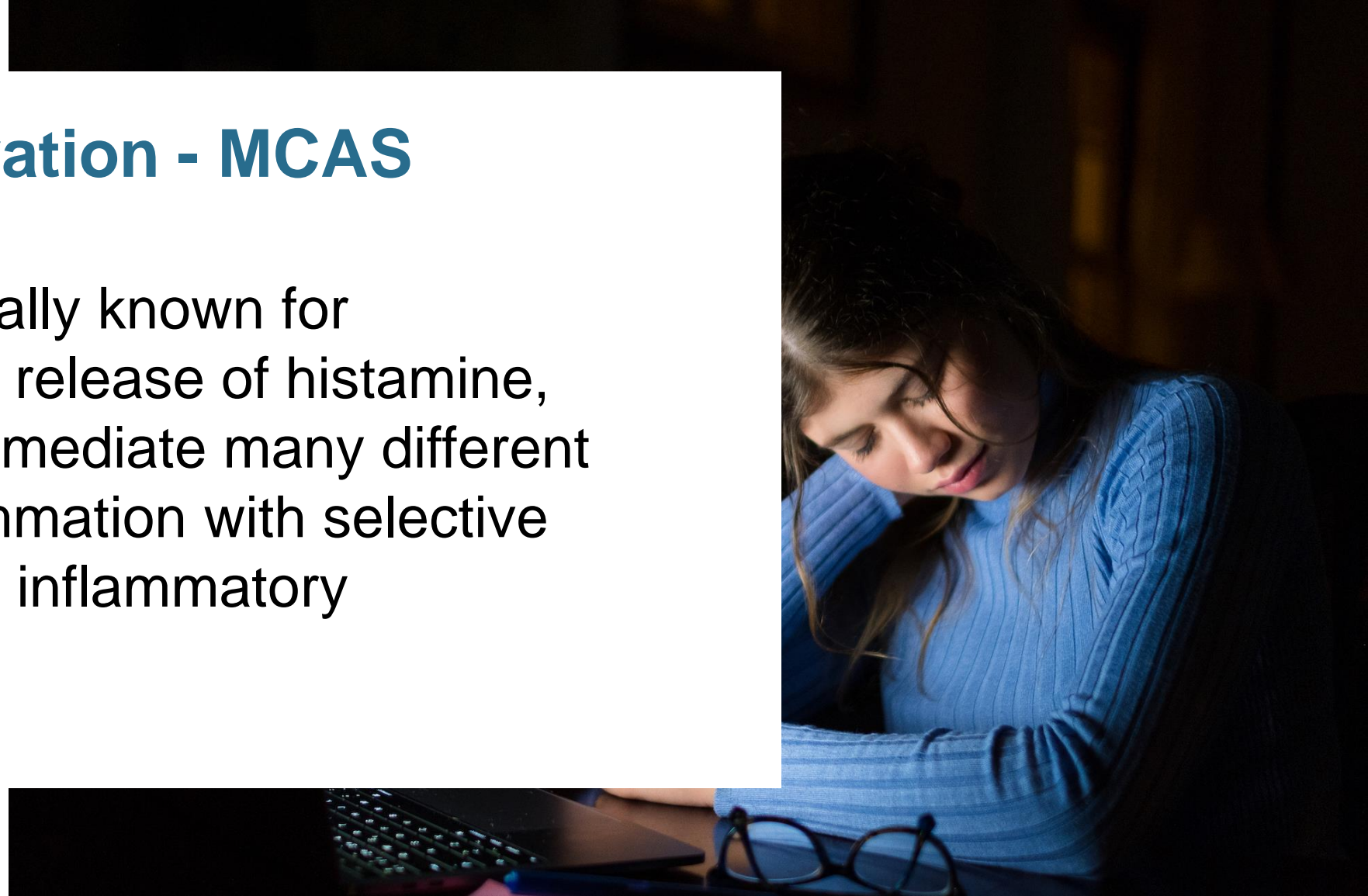


For decades, both MCAS [Mast Cell Activation Syndrome] and CI [Chemical Intolerance] patients have been misunderstood, marginalized, and often referred for mental health evaluation [6, 42, 43], with practitioners assigning diagnostic labels such as Somatic Symptom Disorder, Multiple Chemical Sensitivity (MCS), or Idiopathic Environmental Intolerances (IEI). Our findings suggest that a vast assortment of chemical exposures may initiate or escalate TILT [Toxicant Induced Loss of Tolerance]/CI via chronic, aberrant MC [Mast Cell] activation.



Mast Cell Activation - MCAS

Mast Cell – originally known for degranulation and release of histamine, but now known to mediate many different pathways of inflammation with selective active excretion of inflammatory cytokines.



Mukai K, Tsai M, Saito H, Galli SJ. Mast cells as sources of cytokines, chemokines, and growth factors. *Immunol Rev.* 2018 Mar;282(1):121-150. doi: 10.1111/imr.12634. PMID: 29431212; PMCID: PMC5813811. Miller, C.S., Palmer, R.F., Dempsey, T.T., Ashford, N.A. and Afrin, L.B., 2021. Mast cell activation may explain many cases of chemical intolerance. *Environmental Sciences Europe*, 33(1), pp.1-15.

Mast Cells in All Areas of the Body

H receptors

H1:- All over

H2:- **Very Prominent in Respiratory Tract**

H3:- **Very Prominent in the Brain and Neurons**

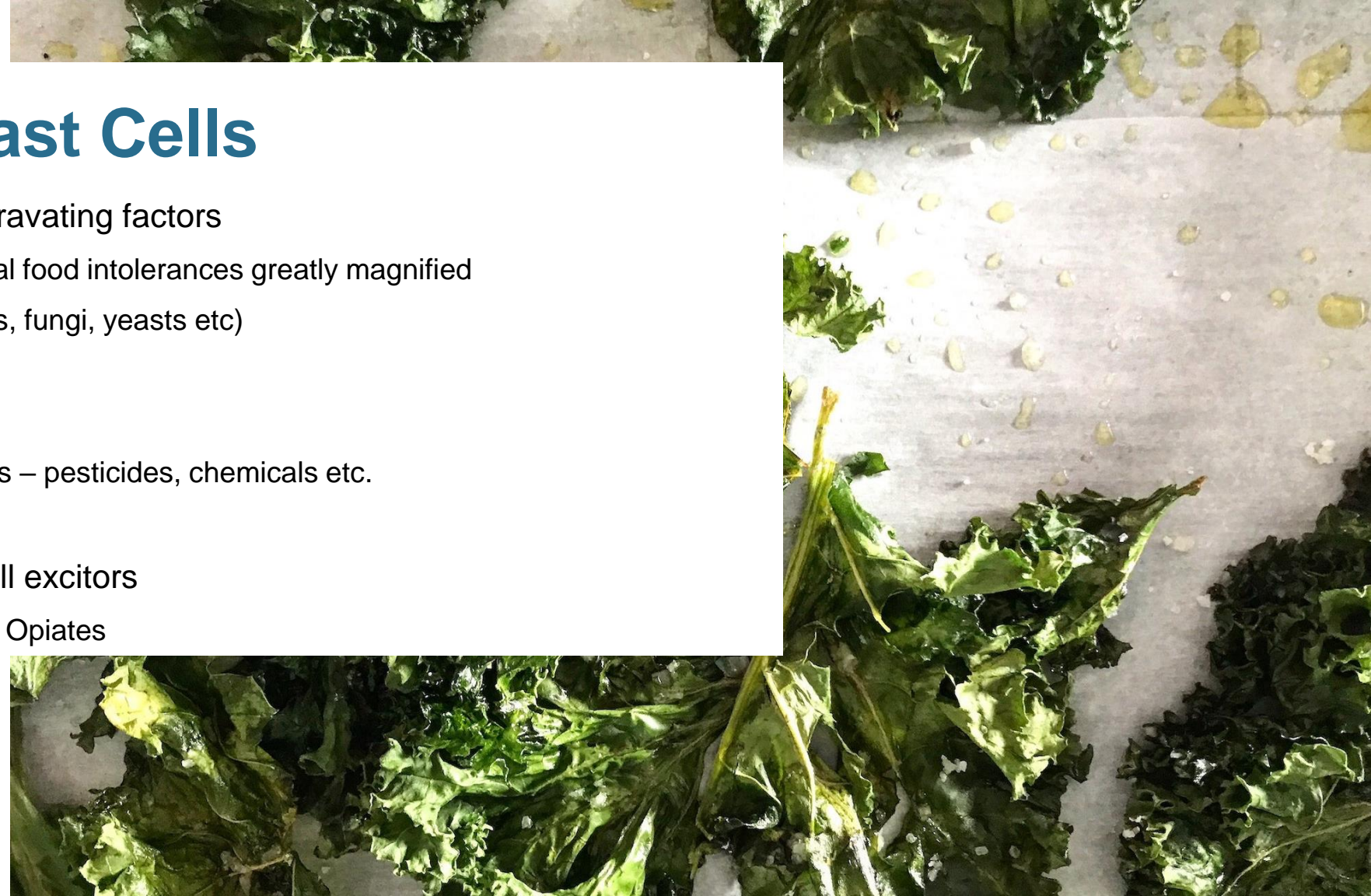
H4:- **Very Prominent in Lymphoid Tissue**





Calming the Mast Cells

1. Removing or reducing aggravating factors
 - Foods - minor and potential food intolerances greatly magnified
 - Microbes (bacteria, viruses, fungi, yeasts etc)
 - EMF
 - Mould
 - Other Environmental toxins – pesticides, chemicals etc.
 - LPS (Leaky Gut)
2. Avoiding universal Mast cell excitors
 - Aspirin, NSAIDs, Alcohol, Opiates



Jiménez, M., Cervantes-García, D., Córdova-Dávalos, L.E., Pérez-Rodríguez, M.J., Gonzalez-Espinosa, C. and Salinas, E., 2021. Responses of mast cells to pathogens: Beneficial and detrimental roles. *Frontiers in Immunology*, 12. Marshall, J.S., King, C.A. and McCurdy, J.D., 2003. Mast cell cytokine and chemokine responses to bacterial and viral infection. *Current pharmaceutical design*, 9(1), pp.11-24.

Mast Cell blockage and suppression

H1R Antihistamines

H2R Famotidine

H3R (Low dose tricyclics, Gen 1 antihistamines, low dose Mirtazapine (1.5-15mg)

H4R

Suppressors:- Quercetin 500-1000mg bd, Montelukast, Na-cromoglycate

Mast Cell H receptor blockage

Gen 2 Antihistamines (H1 blockers)

(Fexofenadine usually the most effective for the most people, but Cetirizine better for some, and Loratadine inhibits Mn ingress into cells, thus “starving” intracellular *Borrelia*. Cetirizine has about a 2% sedation rate). All other bacteria utilise Fe, where *Borrelia* uses Mn.

H2 Blockers - Famotidine, Nizatidine

H2 receptors prominent in acid producing cells in stomach epithelium, and also in respiratory tract/

H3 blockers

– only for research labs so far

The H3R is exclusively expressed in neurones. It is important for homeostatic regulation of energy levels, sleep-wake cycle, cognition, and inflammation.

H4

- Only for research labs

The histamine H4R is expressed on a variety of immune cells as well as on other cells such as spleen, intestinal epithelium, lung, synovial tissue, central nervous system, sensory neurons, and cancer cells (86–94).

H3/H4 blockage – research tools have been:- clobenpropit, thioperamide for H3 and thioperamide for H4. Nothing commercially available, but partial effectiveness from LOW dose Mirtazapine (certainly max 15mg, but some effect noted clinically in 15mgx 0.5, 0.25 and even 0.125 for sleep and anxiety. Also Gen 1 antihistamines, Ketotifen, low dose tricyclic antidepressants, Azithromycin.) H3 antagonists in early trials are targeted against obesity, myocardial ischaemic arrhythmias, cognition disorders, and insomnia

When I have found Mast cell suppression to be useful

- If there are several inflammatory factors operating, the difference noticed by the patient might not be noticeable.
- I have found when the gut reacts frequently and seemingly randomly to different foods:- Na-cromoglycate started early 25-50mg before meals going up to 200-400mg before meals can be helpful.
- Otherwise, when the effects of intolerated foods have been reduced by avoiding them in the diet and the symptoms of infection reduced more than moderately with antimicrobial treatment, the effects of Mast cell blockage and suppression can be noticeable and therefore the patient is motivated to persist with the suppression measures.

A large, stylized microglial cell with a central body and many long, branching processes, rendered in a light blue color against a dark blue background.

Microglial Cells

Microglia

Microglia and Mast cells interact with and provoke each other, and both can become overactive when disturbed by chemicals/toxins, or microbes, either bacterial (e.g. *Borrelia*, *Bartonella*, Strep, Staph, *E coli*, LPS) or viral (SARS-CoV-2, coxsackie, Dengue, HIV, several Hepatitis), also trauma from closed head injury, whiplash, forced restriction of activity.

Skaper, S.D., Giusti, P. and Facci, L. (2012), Microglia and mast cells: two tracks on the road to neuroinflammation. The FASEB Journal, 26: 3103-3117. <https://doi.org/10.1096/fj.11-197194>.


He Y, Appel S, Le W. Minocycline inhibits microglial activation and protects nigral cells after 6-hydroxydopamine injection into mouse striatum. Brain Res. 2001; 909(1-2):187-193. doi:10.1016/s0006-8993(01)02681-6.

Kobayashi, K., Imagama, S., Ohgomori, T. et al. Minocycline selectively inhibits M1 polarization of microglia. Cell Death Dis 4, e525 (2013). <https://doi.org/10.1038/cddis.2013.54>. Nakatomi Y, Mizuno K, Ishii A, et al.

Neuroinflammation in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis: An ¹¹C-(R)-PK11195 PET Study. *J Nucl Med.* 2014;55(6):945-950. doi:10.2967/jnumed.113.131045 .

Dong, H., Wang, Y., Zhang, X., Zhang, X., Qian, Y., Ding, H. and Zhang, S., 2019. Stabilization of brain mast cells alleviates LPS-induced neuroinflammation by inhibiting microglia activation. *Frontiers in cellular neuroscience*, 13, p.191.

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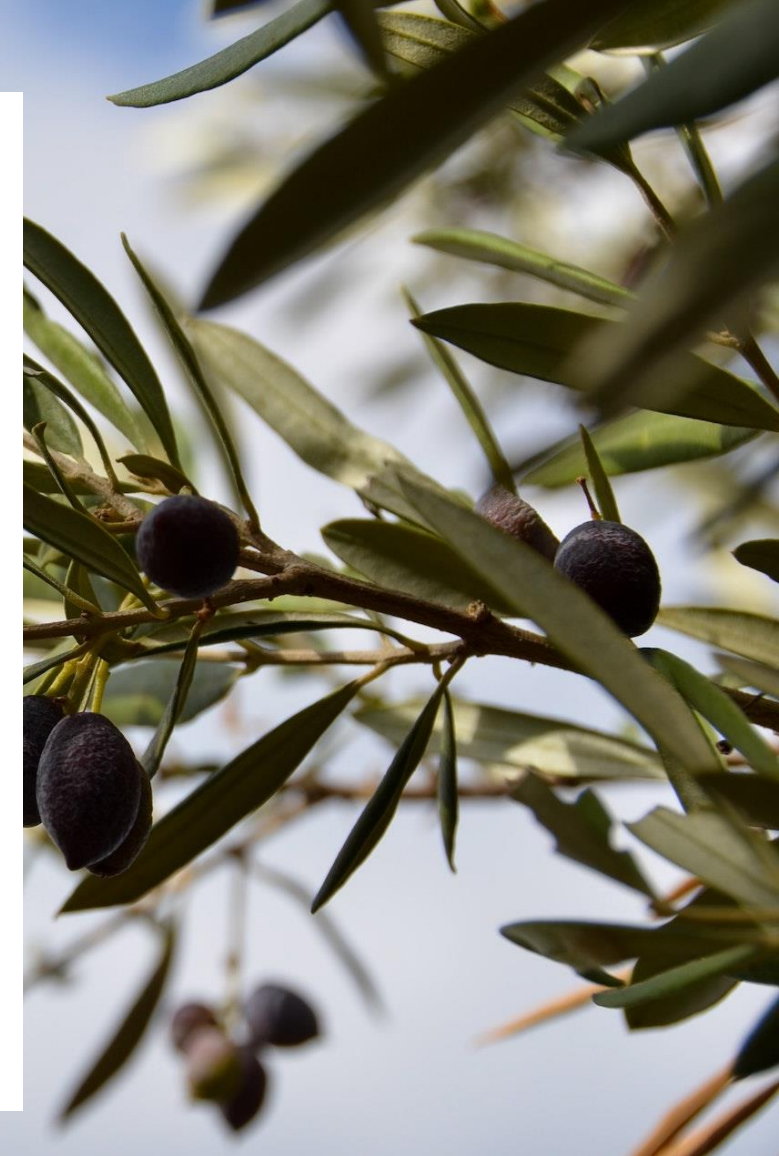
Antimicrobial Treatment to Reduce Burden of Microbes on the System

Olive Leaf Extract

Alternative Medicine Review Volume 14, Number 1 2009

“Olive leaf extract has a beneficial effect on several aspects of cardiovascular disease via its vasodilatory, anti-platelet aggregation, anti-inflammatory, and antioxidant properties.”

“In 1969 researchers demonstrated olive leaf constituents are powerful in vitro inhibitors of numerous viruses, including parainfluenza, herpes, pseudo-rabies, and some forms of polio. Nearly every virus studied, including several cold and influenza viruses, was inactivated when exposed to a constituent of OLE, calcium elenolate.¹⁵ More recently, olive leaf extract was shown to be effective against human immunodeficiency virus (HIV), inhibiting its replication via neutralization of reverse transcriptase and protease.^{15,16} Olive leaf also prevents viral infectivity by inhibiting assembly at the cell membrane, interfering with critical amino acid production, and stopping viral shedding.^{15,17}”



Other Antivirals I Commonly Use

Houttuynia Cordata

All enveloped viruses and Cocksackie. 1:2 liquid, 1-15 drops bd

Inhibits Herpes viruses by blocking NF κ B

Selective Cox-2 inhibitor

Sophora Flavescens (Ku Shen)

Less common, but good for Cocksackie 0.5gm to 3gm tds

CMV and HHV6

Valganciclovir 250mg 2 bd. Currently available in Australia, but expensive. Script must be private, and evidence of CMV might be needed – e.g. Elispot Positive.

Most viruses & Plasmodia

Nitazoxanide 500-1000mg bd

For Herpes Viruses 1-4

Valaciclovir 500mg

1 tds for first day or two. If fatigue, Jarisch-Herxheimer reaction, drop back to 1 daily for 1 week, 2 daily for 1 week, 3 daily for 1 week, the 2 tds for a week or two to determine response.

Settle on 1 tds for some weeks and maintain on 1 bd. If after ceasing after some time there is no deterioration, it could reasonably assumed the Herpes virus has been sufficiently suppressed, and Valaciclovir could be stopped

Li J & Li J: Anti-inflammatory functions of Houttuynia cordata Thunb. and its compounds: A perspective on its potential role in rheumatoid arthritis (Review). *Exp Ther Med* 10: 3-6, 2015

Rossignol, J.F., 2014. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral research*, 110, pp.94-103.

Cocohoba, J.M. and McNicholl, I.R., 2002. Valganciclovir: an advance in cytomegalovirus therapeutics. *Annals of Pharmacotherapy*, 36(6), pp.1075-1079.

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Saeed Khoshnood, Maryam Shirani, Amine Dalir, Melika Moradi, Mohammad Hossein Haddadi, Nourkhoda Sadeghifard, Faezeh Sabet Birjandi, Ilya Yashmi, Mohsen Heidary, Antiviral effects of azithromycin: A narrative review, *Biomedicine & Pharmacotherapy*, Volume 147, 2022, 112682, ISSN 0753-3322, <https://doi.org/10.1016/j.biopha.2022.112682>.

Rossignol, J.F., 2014. Nitazoxanide: a first-in-class broad-spectrum antiviral agent. *Antiviral research*, 110, pp.94-103.



Babesia/ Bartonella



Babesia Symptoms

Clinical Babesia

1. Breathlessness at rest, air hunger
2. Chest pain or tightness
 - High retrosternal chest pain
 - Low chest band of pain or tightness
3. Vivid dreams
4. Multiple tiny haemangiomata on trunk, mostly frontal (tiny cherry red spots)
5. Night sweats, or drenching day sweats.
6. Dark urine/haematuria
7. Spontaneous bruising



Bartonella Symptoms

Clinical Bartonella

1. CNS:- irritability, rages; sensitivity to cold, light, noise, smells;
 - depression, anxiety, panic attacks
2. Difficulty getting off to sleep
3. Convulsions
4. Pain, generalised or severe, “bone pain”
5. Severe oesophageal reflux, gastritis, lower abdominal pain
6. Painful soles of feet, “like walking on rocks, gravel, marbles or broken glass”
7. Striae
8. Recurring lymphadenopathy, sore throat
9. Swelling of knees and/or ankles
10. Fluid retention and especially Lymphoedema
11. Tender subcutaneous nodules, especially along the forearms or lateral thighs
12. New spider telangiectasiae (spider veins).
13. Give-way weakness, (e.g. hand dropping things, knee giving way)

Bowel Parasites

- If a parasite is found in the stool, Blastocystis, Dientamoeba or Giardia can impair cellular immunity, and should be dealt with first prior to other antimicrobial therapy.
(personal communication Prof Kenny De Meirleir, ME/CFS researcher)
- I use Tom Borody's protocols commonly using 3 or 4 antibiotics. These can be found on the website of Sydney Compounding Chemist
- A common alternative is Paromomycin 500mg tds. This is usually regarded as non absorbable, but a chronically sick patient usually has increased intestinal acidity and permeability ("Leaky Gut") and I have sometimes observed Jarisch-Herxheimer reactions from non absorbable antibiotics such as oral Vancomycin or Gentamycin used for improving gut microbiota balance.

Antibiotics

Minocycline:-

- Inhibitor of protein synthesis, 30S ribosome.
- Good brain penetration (56% vs 14% for Doxycycline), more lipid soluble so can cause
- Vestibular disturbance in higher doses, but 100mg bd is usually ok.
- Reduces microglial activity and indirectly reduces Mast cell activity.

Cunha, B.A., 2000. Minocycline versus doxycycline in the treatment of Lyme neuroborreliosis. *Clinical Infectious Diseases*, 30(1), pp.237-238.

Azithromycin:-

- Inhibitor of protein synthesis, 50S ribosome
- Mucolytic (biofilm disperser)
- Good brain penetration (but negligible in CSF or vitreous humour)
- Anti-viral activity in high doses.
- Modulates some inflammatory cytokine expression.
- Jaruratanasirikul, S., Hortiwakul, R., Tantisarasart, T., Phuenpathom, N. and Tussanasunthornwong, S., 1996. Distribution of azithromycin into brain tissue, cerebrospinal fluid, and aqueous humor of the eye. *Antimicrobial agents and chemotherapy*, 40(3), pp.825-826.
- Khoshnood, S., Shirani, M., Dalir, A., Moradi, M., Haddadi, M.H., Sadeghifard, N., Birjandi, F.S., Yashmi, I. and Heidary, M., 2022. Antiviral effects of azithromycin: A narrative review. *Biomedicine & Pharmacotherapy*, 147, p.112682.
- Krickler, J.A., Page, C.P., Gardarsson, F.R., Baldursson, O., Gudjonsson, T. and Parnham, M.J., 2021. Nonantimicrobial Actions of Macrolides: Overview and Perspectives for Future Development. *Pharmacological Reviews*, 73(4), pp.1404-1433.

Other Antibiotics

Pyrimethamine

Inhibits the dihydrofolate reductase of plasmodia. Same mechanism of action as Trimethoprim, but more efficient. Sulfadiazine no longer readily available to complement its activity. Less likely to have negative effect on renal function.

Effective in practice for other bacteria including Bartonella (as can be Co-Trimoxazole. More effective against protozoa if serum folate is not high.)

Rifampicin

Inhibits DNA-dependent RNA polymerase activity by forming a stable complex with the enzyme, suppressing initiation of RNA synthesis.

Used in Tuberculosis. Some intracellular life cycle forms of Bartonella have similarities to Mtb, with mould like properties.

Through RNA polymerase inhibition it also has antiviral properties.

Panayiotakopoulos, G.D. and Papadimitriou, D.T., 2022. Rifampicin for COVID-19. *World Journal of Virology*, 11(2), p.90.

Antibiotic “Helpers”- Hydroxychloroquine and Amantadine pH and Lipids

Most intracellular infections are harboured in parasitophorous vacuoles.

It seems when a microbe passes through a cell wall it coats itself in cell wall membrane which becomes its vacuole.

The organism can then multiply inside the vacuole.

Some organisms show a propensity for existence and better replication if the pH is lower (e.g. *Coxiella*, *Chlamydiae*).

Coxiella (and probably others) multiplies much less if the cholesterol level is high.

(Death by infection from one large review is noted to be much less common in individuals with a raised cholesterol level.)

Hydroxychloroquine (Plaquenil) and Amantadine (Symmetrel) break open these vacuoles.

Plaquenil helps to neutralise the acid, raising the pH of the acidic vacuoles it breaks open.

Biofilm

According to Prof Garth D Ehrlich of Drexel University Pennsylvania, chronic infections *always* involve some biofilm (as well as multiple organisms).

Amount of biofilm can vary greatly.

Horowitz recommends three together:-

Monolaurin (a derivative of Lauric acid)

I use Ecological Formulas Monolaurin 600 1 bd

Stevia (alcohol extract of leaves) 20-30drops bd (www.myherbs.net)

Both of these have anti-Borrelia activity.

Serrapeptase 250,000u bd (particularly effective for endothelial biofilm), can produce Herxheimer-like reactions – presumably as bugs are released from biofilm.

Lumbrokinase is reputed to be quite powerful, but also expensive.

NAC (N-acetyl-cysteine)

New powerful biofilm dispersing agent in final stages of development and trials in W.A.

New Biotech company – Lixa; Biofilm busting candidate:- Neo-X (already in human use, being repurposed)

<https://drexel.edu/medicine/faculty/profiles/garth-ehrllich/>

Some antimicrobial protocols I use.

Initiation of antiviral Therapy

1. Olive Leaf Extract 3gm dry leaf equivalent capsules, Thompson's 5gm organic caps or equal amount of liquid, each 3gm=50mg Oleuropein, 5gm caps contain 100mg Oleuropein
2x3gm caps or 5-6gm (100mg Oleuropein) twice a day. (3 times for acute virus)
(or Viraforce 1 + Olive leaf 3gm of more 1 twice a day)
2. Start Valaciclovir 500mg tablets. First 1-2 days take 1 tablet 3 times a day. If this does not make you tired, take 2 tabs 3 times a day for 8 days., If that has no effect, positive or negative, go back to 1 tab three times a day. Note any reactions or symptoms and let me know. Then if you react with fatigue to 3 per day, take 1 per day for a week, then 1 tab twice a day for a week, then 1 tab 3 times a day. Then 2 tabs 3 times a day. If there is benefit, stay on this dose for a month, then reduce to 1 tablet twice a day. If no reaction, stay on 3 per day until next doctor visit.
3. Start Houttuynia cordata (usually in liquid form 1:2; Can be from Zhang labs HH or HH2 capsules.).
If 1 drop causes a severe Herxheimer reaction, make the first dose 1 drop in half glass of water, the first dose being a sip of that. Increase the dose from there gradually until you are taking 15 drops, (or maximum tolerated dose) twice a day.
4. Nitazoxanide 350-500mg twice a day depending on weight, Can be increased to 500mg tds, or 1000mg bd

PDFs of some of my antimicrobial regimens to follow

- After chronic infections have been dealt with to produce a significant improvement, and improvement has slowed, it is common to see much increased response to Mast Cell suppression and also good response to low dose Naltrexone to modify or reduce autoimmune reactions.
- When a patient has improved on antimicrobials to the extent the only symptoms left are fatigue; and they can lead a near normal life with effort, antibiotics can be stopped and the patient commonly experiences a slow improvement to their peak, even normality after 3 weeks.
- Maintenance therapy in those who deteriorate after ceasing antibiotics can be herbal such as Oregano oil, Cinnamon Bark oil, Jugla nigrans, Scutellaria baicalensis, Cryptolepis sanguinolenta Polygonum cuspidatum and others. Some people just maintain themselves well on Monolaurin 600 1 or 2 (for Borrelia flareups) twice a day.