

# The Candida Covid Connection: Preexisting Candida Overgrowth and Gut Dysbiosis Drives Long Covid

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## Abstract

Long Covid has become a blight, its economic consequences overwhelming. But Long Covid (LC) may represent persistent Covid-19 in those with preexisting Candida overgrowth (CO). The features shared by both are striking. LC may be a growing subset of CO. The altered tryptophan metabolism encountered in LC is driven by IFN- $\gamma$  in reaction to CO. Females are robust producers of IFN- $\gamma$ , yet estrogen promotes CO. The consequent decline in serotonin and melatonin triggers the mood swings and sleeplessness respectively in LC. The low serotonin, the primary messenger in the gut brain axis, creates autonomic dysfunction. The CO induced gut dysbiosis and leaky gut initiate an autoimmune path. TNF $\alpha$  seen in both LC and this opportunistic yeast is at the center of the cytokine triad that leads to neurodegeneration. The Western diet, high in carbohydrates, alcohol, and glutamate, is exploited by this commensal turned parasite. Residual SARS CoV2 and Candida generate abundant ROS, inducing mitochondrial dysfunction. Alcohol tastes different for many with LC, because acetaldehyde requires functioning hepatic mitochondria. This article delves into the complex physiology and biochemistry that drive the symptoms of this conspicuous connection. Recent research has revealed innovative approaches that might address this global scourge, including D-mannose for the immune dysfunction and butyrate for the gut dysbiosis created by and seen in both LC and intestinal Candidiasis.

**Key words:** D-mannose ; butyrate ; acetaldehyde ; serotonin ; autoimmunity

## Introduction

An unholy combination of virus and fungus promoting gut dysbiosis is not new and has been previously reported for HIV[1,2]. Linkage between Candida induced gut dysbiosis and post viral fatigue syndrome has been suspected for almost 30 years[3]. Linkage between CO and not only the immune system[4] but also the gut brain axis is becoming more apparent. Patients with a depleted T-cell count are more prone to Candidiasis. HIV consumes CD4+ T cells and SARS CoV2 consumes CD8+ T cells. This supports reports of CO induced dysbiosis in CFS[3], AIDS, and LC.

The pre-existing Candida associated gut dysbiosis may be undiagnosed in an otherwise healthy individual. Symptoms are nonspecific and fall into a range depending on their severity. Nutritional deterioration in the

Western diet has been insidious. Carbohydrates dominate the menu. Glutamates enhance taste. Alcohol eases the stress. SARS CoV2 has teamed with the commensal turned opportunist *Candida albicans* to mount an increasing challenge to the health of our gut microbiota. The sequestration of the pandemic has amplified the need for alcohol for those dependent. Many of these “light drinkers” and others were already vitamin and micronutrient deficient. The increase in many “modern” diseases is readily apparent - AD, CA[5] and autoimmune diseases[6]. Although the search for a therapeutic solution to LC has been almost frenetic and solutions at times have appeared tantalizingly close, ultimate success has been elusive.

## Discussion

1. Altered tryptophan metabolism (7,8)
2. Increased indoleamine 2,3-dioxygenase activity (7,9,10)
3. Low serum serotonin (11,12,13,14,15,16)
4. Low butyrate produced by gut microbiota (17,18,19)
5. TNF $\alpha$  mediated (20, 5)
6. Oxidative stress associated neurodegeneration (3,21)
7. Elevated dementia triad cytokines - TNF $\alpha$ , IL-1 $\beta$ , IL-6 (22,23,24,25)
8. Low (exhausted) IFN- $\gamma$  (26,27)
9. Low (exhausted) mannose binding lectins (MBLs) (28,29,30,31)
10. Complement mediated fog (29,32,33)
11. High oligomannose glycan shield (34,35,36)
12. Alcohol intolerance (37,38)
13. Dysbiosis, Leaky gut (39,40)
14. Increased autoimmunity (39,40,41)
15. Brain fog and fatigue (29,42)
16. Accelerated AD (43,44,45)
17. More common in females during their reproductive years (46,47)

**Table 1:** Features common to chronic intestinal candidiasis and LC. CO potentiates SARS CoV2 and SARS CoV2 energizes CO. Together they create LC.

The overwhelming majority of those with LC may be those with pre-existing CO and some degree of gut dysbiosis that subsequently contracted Covid-19. CO might be at play in both LC and CFS[3], all mediated by oxidative stress[21].

### 1 Microbiome, Serotonin, Altered Tryptophan Metabolism

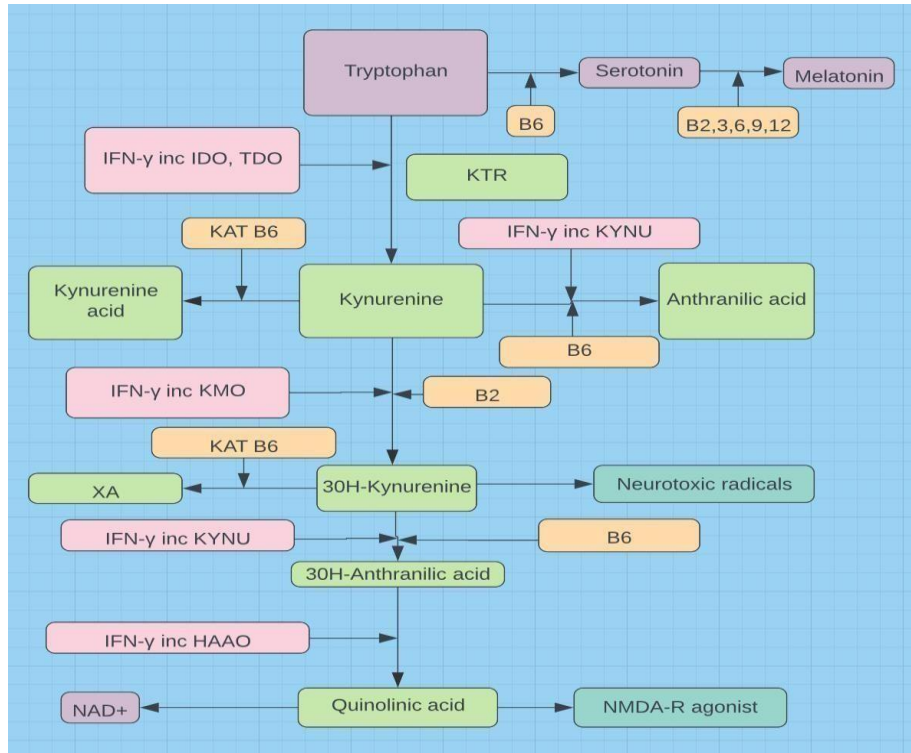
A fungal microbiome has already been established for severe Covid[48]. This gut microbiome may explain the symptomatic overlap between CO and LC. Faecal samples collected in early 2021 from 10 people with COVID-19 showed elevated levels of gut fungi, especially of *Candida* species, relative to 10 healthy[48]. SARS CoV2 induced gut dysbiosis can promote CO[49] and CO induced gut dysbiosis can promote LC[50].

The gut microbiome in those with LC is low in *Bifidobacterium* spp and *Clostridium* spp that produce butyrate[51]. The gut microbiome in those with CO is also low in butyrate producing bacterial species[52].

The vast majority of the body's serotonin comes from intestinal enterochromaffin cells. The altered tryptophan metabolism seen with CO results in a reduction of serotonin (see figure 1). In LC this reduction of serotonin may explain its anosmia and ageusia[53]. These symptoms may be related to the downstream effect of the serotonin induced autonomic imbalance on the gut brain axis. Loss of taste and smell have been well described in LC, but it has also been described post vaccination[54]. One study of 2289 elderly participants reported that those with poor olfaction had a 46% higher cumulative risk for death after 10 years v those with good olfaction[55]. The gut enterochromaffin cells produce 95% of the body's serotonin[16], but rely on the essential amino acid tryptophan from

either diet or intestinal bacteria to produce serotonin. Gut dysbiosis compromises the microbiota balance causing a decrease in critical micronutrients, e.g., butyrate, tryptophan, and dopamine[16]. CO may displace many of these good bacteria with consequent loss of vital micronutrients. The LC microbiome reflects this same loss of micronutrients, especially tryptophan[10]. The effect of decreased serotonin and dopamine on downstream monoaminergic and GABAergic neurotransmission is complex but clearly creates an autonomic imbalance.

T cells produce IFN- $\gamma$  in response to CO[56], which shifts tryptophan metabolism from the serotonin pathway to the kynurenine pathway and NAD<sup>+</sup> production (see figure1). This altered tryptophan metabolism is common to both CO and LC. Low serotonin[11,12,13] and melatonin ensue along with mood swings and insomnia respectively. Reports on IFN- $\gamma$  levels in LC differ. Some report elevated IFN- $\gamma$ [57], while others report marked decreases in IFN- $\gamma$ [26] However, the latter is generally considered to be due to immune exhaustion[16]. Upregulation of indoleamine dioxygenase (IDO-1 and IDO-2), courtesy of IFN- $\gamma$ , is directly related to Covid severity and CO[7,9] and may underlie potential for LC[10]. Females are robust producers of IFN- $\gamma$ . IFN- $\gamma$  in response to CO drives the pivot from the serotonin pathway to the kynurenine pathway[56]. This shift also occurs in LC[10]. Females are robust producers of IFN- $\gamma$  and this prompts upregulation of the kynurenine pathway (see **figure 1**).

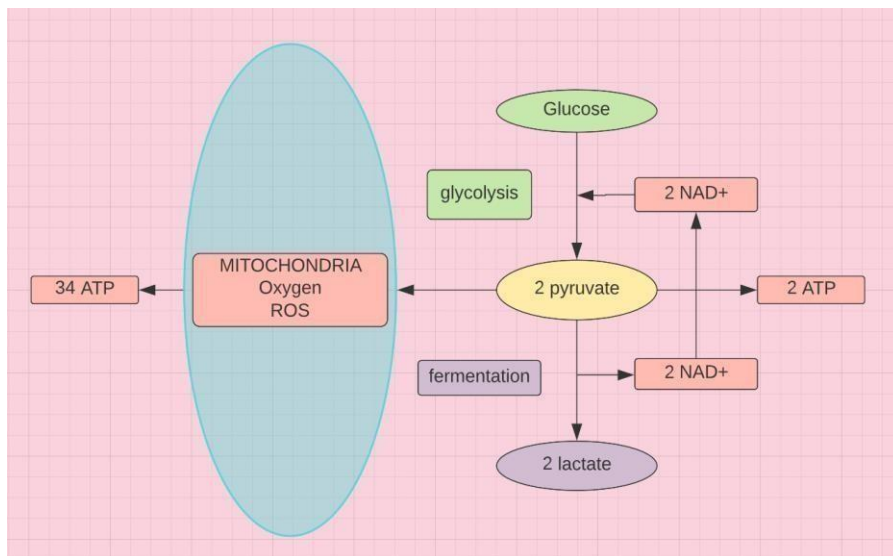


**Figure 1:** The serotonin and kynurenine pathways.

Estrogen reduces the complement response to CO[46], which is more common in females[47].

Quinolinic acid and 3(OH)kynurenine are neurotoxic and upregulated when B6 is deficient[58]. The two NAD<sup>+</sup> produced by the kynurenine

pathway help address the shortfall in ATP due to the oxidative stress induced mitochondrial dysfunction. Candida requires much more thiamine in such an environment[59].



**Figure 2.** ATP production per molecule of glucose drops from 34 to 2 in the environment of severe oxidative stress.

**2 Alcohol and Mitochondria**

Alcohol intolerance is a primary complaint in LC (alcohol tastes different) and CFS. Hepatic metabolism of alcohol by alcohol dehydrogenase yields acetaldehyde, but further degradation by aldehyde dehydrogenase occurs in mitochondria. To control CO the body oxidizes the yeast through granulocytes[60]. Even more ROS are released. When oxidatively

stressed mitochondrial function is further compromised, acetaldehyde can cause headache, hangover, brain fog, fatigue[61].

These symptoms are seen in CO, which produces acetaldehyde from ethanol and/or glucose. The yeast induced acetaldehyde depletes thiamine[62], a deficiency linked to chronic alcoholism and Wernicke Korsakoff syndrome. This is exacerbated by glucose or ethanol

loading[42] and leads to acetaldehyde induced brain fog. SARS CoV2 induced increases in acetaldehyde post Covid-19 may suggest the presence of early LC. Could a glass of wine diagnose LC?[37].

Although some reports suggest benefit from light alcohol intake against vascular dementia, there is no such efficacy against AD[63]. The brain fog of alcohol induced acetaldehyde (hangover) is equivalent to that induced by chronic intestinal candidiasis after glucose loading[48].

Thiamine deficiency, often encountered with excessive ethanol intake, is a required cofactor for pyruvate dehydrogenase. Without this enzyme pyruvate is shunted from producing acetyl CoA (requires vitamin B5 aka pantothenate) to lactate instead. Several other dehydrogenases in the Krebs Cycle also require thiamine pyrophosphate (TPP). These two thiamine-dependent pathways may mediate mitochondrial dysfunction and its associated fatigue. Thiamine deficiency rates range from 20% to over 90%[64].

CO is marked by increased production of ROS by the fungus[65] and by the host. SARS CoV2 can only aggravate this increase in ROS with concomitant loss of mitochondria and decrease in oxidative phosphorylation[66]. Susceptible individuals may already have an antioxidant shortfall

Persistent spike protein[67], demonstrated in those with LC, creates a nearly insurmountable challenge. Secondary neurodegenerative changes in an organ highly dependent on oxygen may accelerate[68], when combined with minimal alcohol abuse and thiamine deficiency[38]. *Candida albicans* is able to generate significant amounts of reactive oxygen species (ROS)[65]. In order to avoid lysis this forces cells to curtail their own ROS production from mitochondrial oxidative phosphorylation. The kynurenine pathway produces NAD<sup>+</sup> via a non oxidative pathway, requiring B2 and B6, to create ATP (see figures 2,3). B1 is required for both oxidative phosphorylation and the pentose phosphate shunt, which bypasses the mitochondria to produce NADPH and ultimately ATP. This latter is especially important for erythrocytes, which lack mitochondria.

### 3 MBLs, Brain Fog, and Amyloid

MBLs are an integral part of innate immunity, the first line of defense, while antibodies comprise the bulk of adaptive immune defense. *Candida*[35], SARS CoV2, and many types of cancer cells are protected by high mannose glycan shields to avoid exposure to immunoglobulins. SARS CoV2, its vaccine, and 31 different types of cancer cells produce a CD147 epitope[69] that is adorned by a high oligomannose glycan shield. This oligomannose glycan shield on *Candida albicans* and SARS CoV2 attracts MBLs, which are vital to fungal elimination[31]. These oligomannosides not only serve to protect them but also to upregulate TNF $\alpha$ [34,20]. Candidiasis is linked to low MBL[28,29,30,31].

Recurrent Covid-19 is also linked to low MBL[32], generally felt due to immune exhaustion. The protective benefit of the oligomannose glycan shield in avoiding immunoglobulin detection is evident when MBLs are low[70]. Low MBLs may mark the onset of brain fog in LC[29]. Brain fog early in CO may be glucose or ethanol induced and acetaldehyde mediated, but the more serious cognitive decline that develops later may be MBL/lectin complement pathway[33] and cytokine mediated.

Covid-19 and its vaccines present the CD147 epitope and its oligomannose glycan shield. The MBL assault triggers the complement and clotting cascades. The ensuing MBL induced microthrombosis, closely linked to d-dimers, may be the prelude to neurodegenerative disease. The presence of amyloid beta like peptides in microglia

associated with candidiasis (27,49), already demonstrated in AD, and the linkage of Covid-19[44,45] and CO with neurodegenerative symptoms paints a worrisome long term picture for some long haulers. Brain amyloid  $\beta$  (A $\beta$ )-like peptide aggregates characterize multiple *Candida*-associated neurodegenerative conditions, including Alzheimer's disease[43]. Amyloid precursor protein surrounds cleaved amyloid beta (A $\beta$ ) peptides around the CNS yeast cells. This activates NF- $\kappa$ B and induces production of IL-1 $\beta$ , IL-6, and TNF $\alpha$ [22]. This triad can activate NF- $\kappa$ B and NF- $\kappa$ B can activate the triad[23]. This triad has been detected in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, and acquired immunodeficiency dementia[24].

### 6 Leaky Gut and Autoimmunity

The leaky gut syndrome induced by both Covid 19[71] and CO[39] induces an environment that promotes autoimmune disease[40,41], e.g., T1DM[72]. Post vax T1DM has also been reported[73,74]. CO can also induce T2DM[75,76], as can LC, but both types increase risk of CO. Both also increase risk for LC. There are numerous reports of T1DM appearing immediately post vax. Other reports claim that the vaccine protects against developing T2DM post Covid-19, but are silent regarding T1DM. Autoimmune T1DM post vax is well described(73,74,76). CO is linked to leaky gut and leaky gut is linked to autoimmunity. LC has now been classified as an autoimmune disease[6]. The balance between leaky gut and autoimmunity is precarious[77].

### Prevention and Therapy

Many experienced clinicians advocate significant dietary changes to eliminate CO, i.e., the *Candida* cleanse detox. But changing one's diet can be more difficult than changing one's religion. Fortunately there may be other recently discovered approaches that cover LC as well, including D-mannose, butyrate, and tryptophan/serotonin/melatonin. Vitamin D, magnesium, and the active forms of the B vitamins, especially B1, B2, B3, B6 have proven efficacious. Prebiotics and probiotics in mild cases to fecal transplants in more severe cases have also been recommended.

#### 1 Mannose

D-mannose, usually prescribed for UTI, suppresses TNF $\alpha$ [78], central to the dementia induced by the triad of TNF $\alpha$ , IL-6, IL-1 $\beta$ [24]. TNF $\alpha$  (inhibits mannosidase) is also central to the synthesis of the high oligomannose glycan shields on both *Candida albicans* and SARS CoV2, not to mention 31 different types of cancer cells[69]. TNF $\alpha$  upregulates IL-1 $\beta$ , linked to autoimmune disease. Mannose suppresses IL-1 $\beta$ [79]. Mannose may be especially helpful in preventing leaky gut syndrome[80,81], tightly linked to autoimmune disease. In fact, beneficial applications of mannose are rapidly expanding. D-Mannose offers newly recognized efficacy for diabetes, obesity, lung disease, autoimmune diseases and recently anti-tumor activity[82]. Once considered ill advised for diabetics, it has now been heralded as beneficial for diabetics.

#### 2 Butyrate

Butyrate opposes growth of pathogenic yeast[18] and appears to increase serotonin, especially in the hippocampus[83]. Serotonin actively attenuates fungal virulence[84]. AD related amyloid beta bodies are well described in the hippocampus and amyloid beta bodies are linked to *Candida*[22,43]. SB exerts significant antifungal activity on pathogenic yeasts[17]. Short chain fatty acids, especially butyrate, suppress IDO and increase serotonin (see figure 1)[85,86].

#### 3 Serotonin and tryptophan

The altered tryptophan metabolism creates a significant serotonin shortfall. Serotonin supplementation can help fill the void. It attenuates fungal virulence[14,15] and may restore a proper immune response[87]. Less of the essential amino acid tryptophan is supplied by gut microbiota during LC and CO. Many clinicians encourage supplementing with tryptophan[88].

#### 4 Vitamin D and magnesium

Men with the highest compared to lowest 1,25(OH)<sub>2</sub>D and activation ratios, i.e., active form/storage form (1,25(OH)<sub>2</sub>D/25(OH)D), are more likely to possess butyrate-producing bacteria associated with favorable gut microbial health[89]. Vitamin D, low in both LC and CO, suppresses TNF $\alpha$  [90,91]. Vitamin D levels are inversely correlated with TNF $\alpha$ . Vitamin D is also a fungicide effective against *Candida albicans*[92,93]. Vitamin D modulates the immune actions of IFN- $\gamma$ [94].

Magnesium, a required cofactor for many enzymatic steps in the synthesis of vitamin D, also suppresses the neurodegeneration-inducing triad of TNF $\alpha$ , IL-1 $\beta$ , and IL-6[95]. This cytokine triad drives LC and candidiasis[24,25,26,27] and neurodegenerative disease in general[25].

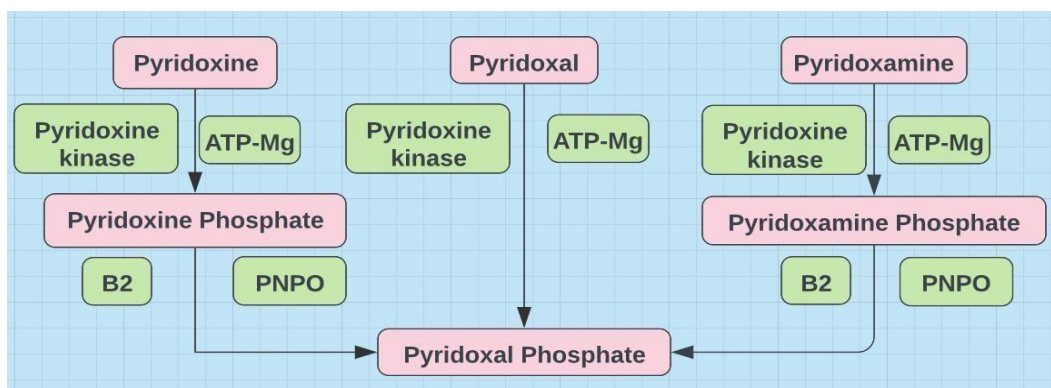
#### 5 Covid boosters

Covid boosters are a personal choice, but the latest data are worrisome. Boost at your own risk. Each boost increases the likelihood of a

recurrence and the associated risk of LC[96]. The CD147 epitope is present on the spike proteins S of the virus and its vaccines[97,98]. Post vax autoimmune complications include T1DM, CFS, multiple sclerosis, alopecia, Bell's palsy, Guillain-Barré syndrome, immune thrombocytopenia, rheumatoid arthritis[99]. Post vax neurological complications were seen in 31.2% of 19,108 post Covid vaccinees[100]. Post vax microthrombosis is the most well known complication, especially amongst our athletes. MBL activity is strongly correlated with d-dimers[102]. D-dimers were reported in 62% of 900 Covid vaccinees[102].

#### 6 Vitamins

Gut microbiota is responsible for the production of several water-soluble vitamins, including biotin, folate, niacin, ascorbate, riboflavin and thiamine. Gut dysbiosis results in a reduced amount of such vitamins[103]. Some vitamins modulate the gut microbiome by increasing the abundance of presumed commensals (vitamins A, B<sub>2</sub>, D, E, and beta-carotene), increasing or maintaining microbial diversity (vitamins A, B<sub>2</sub>, B<sub>3</sub>, C, K) and richness (vitamin D), increasing short chain fatty acid production (vitamin C), or increasing the abundance of short chain fatty acid producers (vitamins B<sub>2</sub>, E). Others, such as vitamins A and D, modulate the gut immune response or barrier function[104]. Thiamine (B<sub>1</sub>) deficiency can cause[105] or be caused by gut dysbiosis[69,106].



**Figure 3.** Pyridoxal phosphate (P5P) is the active form and requires B2 and magnesium for synthesis.

B<sub>2</sub> is a required cofactor to produce the active form of B<sub>6</sub> (see figure 3). The vast majority of B Vitamin supplements contain the inactive pyridoxine. P5P, the active form of B<sub>6</sub>, decreases inflammatory cytokines, including TNF- $\alpha$  and IL-6[107].

#### Conclusion

Any strategy that limits the production of TNF $\alpha$  has multiple benefits. This cytokine inhibits mannosidase and limits mannose trimming in the Golgi. Suppressing TNF $\alpha$  suppresses the “triad”. This triad is central not only to neurodegenerative changes but also to processing the high oligomannose glycan shield present on invading pathogens and many types of cancer cells. Improving the suboptimal gut microbiome should address CO, LC, and the leaky gut associated with autoimmune disease. This opens a new approach to treatment of autoimmune disease, one that bypasses specifically designed inhibitors e.g., Janus kinase inhibitors for vitiligo[108]. Vitiligo is characterized by a microbiome that lacks butyrate producing bacteria and that is less rich and less diverse than that of healthy controls[108]. The myriad benefits of a broad approach, one that may improve the gut microbiome and limit the “triad” without a major dietary makeover, are alluring.

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