Immune Health in the Era of Pandemics

Tieraona Low Dog, MD

Chair: US Pharmacopeia Dietary Supplement Admissions, Evaluation and Labeling Expert Committee

Clinical Assoc. Professor of Medicine University of Arizona (retired)

National Geographic's
Life Is Your Best Medicine
Healthy At Home
Fortify Your Life
Guide to Medicinal Herbs

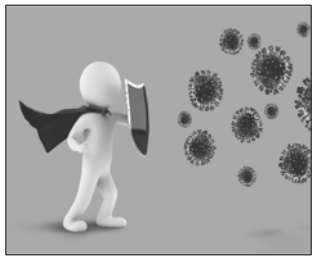
Co Editor Oxford University Press:
Integrative Women's Health

www.DrLowDog.com

Welcome

- We are about to take a journey into one of the most **amazing and marvelous systems in the human body**…**the immune system.**
- **Beautifully designed**…**artful and complex**…it has been developed over the span of human existence to protect us from **infection**, **remove cellular debris** and waste, **seek out and destroy abnormal cells**, and allow us to **live in relative harmony with our environment.**
- We'll start with some definitions and terminology and then work our way through the impact of **nutrition, micronutrients**, the gut **microbiota, stress and sleep in prevention and management.**

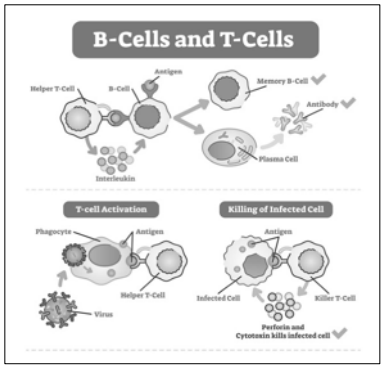
Innate Immune Response



- **First line of defense**, immediate and nonspecific.
- **Lacks immunologic memory.**
- Phagocytes (macrophages), complement, and cytokines.
- **Anatomical barriers:**
  - **Skin** strong physical barrier
  - **Sweat and tears** contain lysozymes that inhibit bacterial growth
  - **Cilia in nose and lungs trap microbes/viruses**
  - **Cough and sneezing** dispel microbes
  - **Stomach acid** destroys many microbes and viruses
  - **Microbiota compete for space/nutrients**
  - **Cross talk between intestinal microbiota and immune cells**

Adaptive Immunity

- **Second line of defense**, takes days or weeks to develop. Immunologic "**memory**."
- **B cells produce antibodies**—target pathogen, then macrophages destroy. Also called "humoral" immunity.
- **T-cells** part of cell-mediated response.
  - **Killer T** cells directly attack/kill infected cells.
  - **Helper T** cells enhance immune response.
  - **Regulatory T cells** suppress immune response.



- **1918-19 H1N1 "Spanish flu":** 500 million people infected; **50 million died globally, 675,000 people in US.** Highest death rate **15–34 years age.**
- **1957-58 H2N2**: **1.1 million deaths globally, 116,000 in the US.**
- **1968 H3N2: 1 million deaths globally, 100,000 in US, mostly in people over 65 years old.** This virus continues to circulate.
- **2009 H1N1**: **60.8 million cases,** 274,304 hospitalizations, **12,469 deaths** in US. **80% of deaths were in those < 65 years of age.**
- Note: all these pandemics were caused by **influenza A viruses.**

www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html

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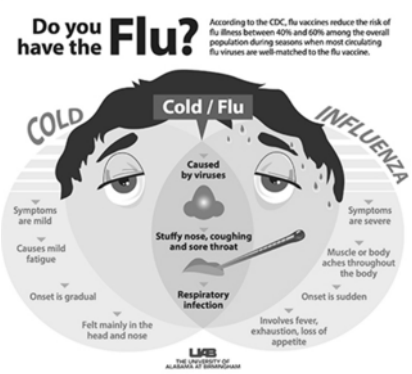
The Flu

- Yearly seasonal influenza: **3-5 million severe cases and 300,000–650,000 deaths globally.**
- Influenza **2017-2018 US**: ~45 million cases, 21 million medical visits, 810,000 hospitalizations, and **61,000 deaths. 182 pediatric deaths.**
- Influenza **2019-2020 US**: estimates **39–56 million cases**, 410,000–740,000 hospitalizations, **24,000–62,000 deaths.**



https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm

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Severe Acute Respiratory Syndrome (SARS)

- **SARS** coronavirus first reported February **2003 in Asia**: 8,098 people worldwide became sick; **774 died.**
- **SARS-COV2** virus (COVID 19): 518M cases, 6.2M deaths globally; 81M cases and 995K deaths in US (as of May 11, 2022)
- Symptoms: **fever, cough, shortness of breath, fatigue; sore throat, headache, nausea/vomiting/diarrhea, loss of taste or smell.**
- Risk groups: age **>65 years**; **underlying health conditions** (lung or heart disease, diabetes, immune-compromised), **obese** individuals (BMI >30), African/Native/Hispanic Americans.

https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747/all/Coronavirus_COVID_19__SARS_CoV_2_#4.0

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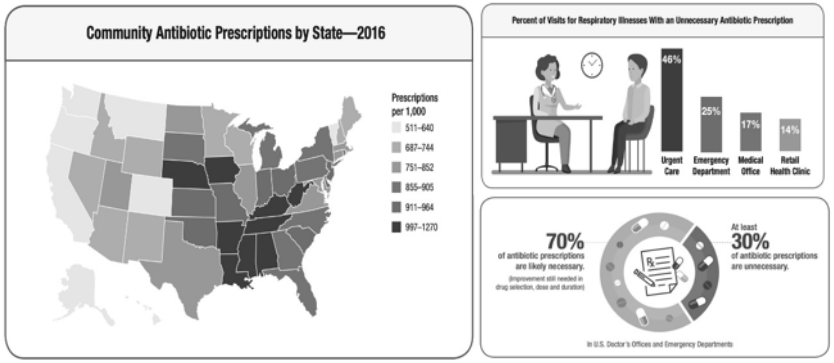

https://www.cdc.gov/antibiotic-use/stewardship-report/pdf/stewardship-report-2018-508.pdf

CDC: Antibiotic Resistance Threats in US, 2019

- **~Every 11 seconds someone gets antibiotic resistant infection**—and **every *15 minutes, someone in the US dies.***
- In addition, 223,900 cases of *C. diff* in 2017; at least **12,800 people died.**
- Current bacteria/fungal threats to human health:
  - **5 are "*urgent threats*"**
  - **11 are "*serious threats*"**
  - **2 are "*concerning threats*"**
  - **3 more on the "*watch list*."**

When to Seek Help

- Fever in child **younger than 3 months of age**
- **Fever that lasts more than four days**
- **Child with fever of 104 F** or higher that doesn't come down **within 2 hours after using fever reliever** (children 3 mo-3 years often run temps up to 102.5 and up to 103 if older—this is okay if eating, drinking, easy to wake, etc.)
- **Difficult, rapid or labored breathing**; skin appears **bluish**
- **Bloody diarrhea** or **severe abdominal pain** that worsens with jumping up/down
- Fever with **stiff neck, bad headache, and/or rash** that doesn't fade when pressed
- **No pee for 6 hours, no wet diaper in 8 hours,** no tears—signs of dehydration

Special Populations: Elders

- Many elders have **lower body temperature and poor ability to mount fever.**
- **Loss of appetite,** mental changes, **confusion**, **fatigue, weight loss,** red inflamed skin, new onset **incontinence** or **increased urination**, blood in urine, **shortness of breath**, new onset or increased **pain,** new or change in **cough** can all suggest **serious infection.**

Other Special Populations

Fever in any of the following should **warrant attention** of health care provider:

- Anyone undergoing **cancer treatment**
- Anyone taking medications that **suppress the immune system**
- Underlying serious illness such as **heart failure, kidney/liver disease**
- **Pregnant with a fever over 100.5 F**

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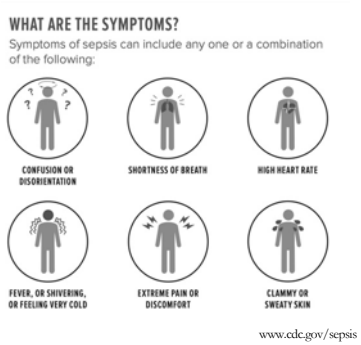
Sepsis: A Big Problem

- Anyone can become septic. Risk factors include:
  - **Diabetes, lung/kidney disease; cancer**
  - **Adults 65 or older**
  - People with **weakened immune systems**
  - **Children** younger than **one year old**
  - Most frequent organisms associated with sepsis: *Staphylococcus aureus* (staph), *E. coli.*
- ***~270,000 Americans die of sepsis every year, nearly 1:3 patient deaths in hospital***



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Nutrition can play major role in **"individual susceptibility"** to **bacterial or viral infections and, if infected, in course and outcome of disease.**

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Ultra-processed Foods

- It is important to ***dramatically reduce*** consumption of **ultra-processed foods**—industrial foods with little/no intact foods, and often high in **added sugars, salts, artificial flavors, colors and other additives.**
- Individuals with **highest vs. lowest** intake of ultra-processed foods had a **31% increased likelihood of death** after adjusting for confounders.[1]
- In US: **57% of total calories for adults**[2] and **67% of total calories for children**[3] come from these foods.
- Dietary **protein, fiber, vitamins A, C, D, E; zinc**, **potassium** and **magnesium** decreased significantly; added **sodium, carbs, sugars, and saturated fats** increased with **highest intakes** of ultra-processed foods.[4]

1. Kim H, et al. *Public Health Nutr* 2019; 22(10):1777-1785. 2. Juul F, et al. *Am J Clin Nutr* 2022; 115(1):211-221
3. Wang L, et al. *JAMA* 2021; 326(6):519-530. 4. Martinez-Steele E, et al. *Popul Health Metr* 2017; 15:6

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Diet and COVID-19

- Although **no study** has shown diet can **prevent or treat** COVID-19, the pandemic has highlighted that **many comorbidities** associated with severe infection are **diet related disease**, such as: **hypertension, obesity, and diabetes.**[1]
- More than **3.8 million-person months of study**, those consuming **highest quality whole food diet** (high intake fruit, veggies and whole grains) had **9% lower risk** of infection, and **41% lower risk of developing severe COVID-19.**

O'Hearn M, et al. *J Am Heart Assoc* 2021; 10(5):e019259.

Merino J, et al. Gut 2021: 70:2096-2104

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Adequate High- Quality Protein

- **Adequate protein** intake is crucial for **optimal antibody production.**
- Low protein (<0.8 g/kg bodyweight) can **decrease immunoglobulins and GALT,** which play a role in **gut-mucosal defense** against infection.
- Protein malnutrition **increases susceptibility to viruses** due to decreased **function of neutrophils**, complement, IgA, and **antibody response**.

Ah O. Protein Energy Malnutrition and Susceptibility to Viral Infections as Zika and Influenza Viruses. *J. Nutr. Food Sci.* 2016;6:2. doi: 10.4172/2155-9600.1000489;

Rodríguez L et al. Malnutrition and gastrointestinal and respiratory infections in children: A public health problem. *Int. J. Environ. Res. Public Health.* 2011;8:1174–1205.

Fulop T, et al. Relationship between the response to influenza vaccination and the nutritional status in institutionalized elderly subjects. *J Gerontol A Biol Sci Med Sci* 1999;54:M59–M64.

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Dietary Fiber

- **Soluble and insoluble.** Necessary for **healthy gut microbiota**, intestinal **barrier** function, keeping **inflammation, cholesterol and blood glucose** in check. Modulate **immune** system, **70% of which is in GI tract**.
- Significant **reduction in hs-CRP concentrations (measurement of inflammation in body)** with increased **fiber (30 g/d) consumption.**
- Dietary fiber inversely **linked** to risk of ***death* from respiratory and infectious diseases.** For **each 10 g/d increase** in dietary fiber:
  - **Mortality-relative risk** from infectious and respiratory diseases decreased by **34% and 18% in men** and **39% and 34% in women**, respectively.

North CJ, et al. *Eur. J. Clin. Nutr.* 2009;63:921–933; Bibbo S, et al. *Eur Rev Med Pharmacol Sci* 2016; Nov;20(22):4742-4749.

Park Y, et al. Dietary fiber intake and mortality in the NIH-AARP diet and health study. *Arch. Intern. Med.* 2011;171:1061–1068.

Partula V, et al. A J Clin Nutr 2020; 112(1): 195-207

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Carbs to Fiber Ratio

- **Carb to fiber ratio:**
  - Higher than 10:1 is poor
  - 6:1 to 10:1 is good
  - 5:1 or less is great
- Corn flakes far left (24:1)
- Kashi GoRise cereal right (~3:1)

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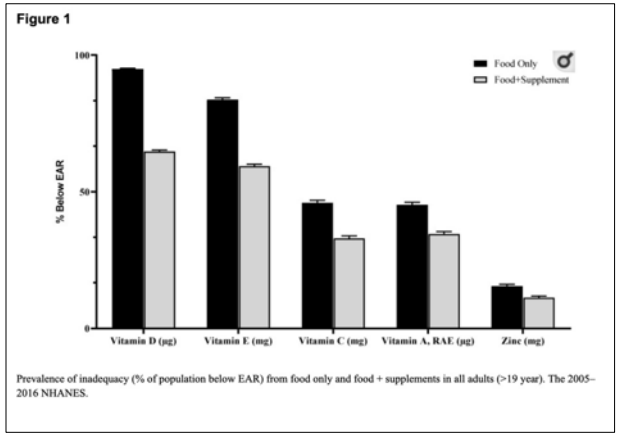

Prevalence of inadequacy (% of population below EAR) from food only and food + supplements in all adults (>19 year). The 2005–2016 NHANES.

Image from: Reider CA, et al. Inadequacy of Immune Health Nutrients: Intakes in US Adults, the 2005–2016 NHANES. *Nutrients* 2020 Jun; 12(6): 1735.

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Fruits and Veggies

- **Minimum** daily recommended **fruit** intake is equivalent to **1.5 cups**
  - **12.3%** adults consume this minimum amount[1]
- **Minimum** daily recommended **vegetable** intake is equivalent to **2 cups**
  - **10%** of adults consume this minimum amount[1]

1. Lee SH, et al. *Morbidity and Mortality Weekly* (CDC) 2022 January 7; 71(1):1-9

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Vitamin A

- The "anti-infective vitamin."
- Critical for **healthy barrier function (skin, lungs, gut).** Modulates *Bifidobacterium and Lactobacillus.*[4]
- Low vitamin A increases risk of lung dysfunction/**respiratory disease**.[1]
- **43 trials:** supplementing children in developing nations **reduces all cause mortality 24%.**[2]
- **45% Americans don't get enough vitamin A with food alone.**[3]
- Vitamin A intake **decreases with age in children**; ***girls and African American kids*** higher risk for low intake.
- Zinc and iron deficiency linked to vitamin A deficiency.

1. Timoneda J et al. Vitamin A Deficiency and the Lung. *Nutrients.* 2018;10:1132.
2. Imdad A, et al. *Cochrane Database Syst.Rev.* 2010, CD008524
3. Reider CA, et al. *Nutrients* 2020: 12, 1735
4. Ferreira C, et al. *Microorganisms* 2020 Oct; 8(10): 1514.

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MAIN FUNCTIONS

- Essential for sight, dim-light adaptation, and color vision
- Supports reproductive health for both men and women
- Required for proper immune function
- Influences cell growth and development

GOOD SOURCES

There are two forms of dietary vitamin A: preformed vitamin A from animal products and provitamin A carotenoids from fruit and vegetables.

Preformed Vitamin A

- Cod Liver Oil, 1 teaspoon, 1,350 µg RAE
- Egg, 1 large, 80 µg RAE

Provitamin A

yellow & orange fruit & vegetables

- Sweet Potato (baked), 1 cup, 1,922 µg RAE

RAE = Retinol Activity Equivalents; µg = micrograms

DAILY RECOMMENDATION

900 µg RAE	700 µg RAE
Men	Women

SPECIAL NOTES

- RAE = a unit of measure for the vitamin A content of food. It reflects the amount of active vitamin A provided by the different types of food sources.
- It is possible to ingest too much preformed vitamin A (retinol). The Tolerable Upper Intake Level (UL) is 3,000 µg RAE of retinol/day.
- There is no UL for provitamin A carotenoids because the liver controls their conversion to retinol.

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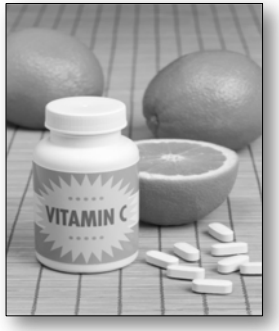
Vitamin C

- Plays crucial role in **innate and adaptive immune responses.**
- **Maintains *epithelial barrier* function, increases alveolar fluid clearance, and attenuates pro-inflammatory response.**
- Deficiency leads to **impaired immunity and greater risk of infection**. [1]
- **Only 1 in 10** Americans get recommended daily intake for **fruits and vegetables.**[2]
- ***~15.7 million* Americans** have serious vitamin C **deficiency; *~60 million*** *have* marginal status.



1. Vorilhon P, et al. *Eur J Clin Pharmacol* 2019; 75(3):303-311.
2.https://www.cdc.gov/mmwr/volumes/66/wr/mm6645a1.htm?s_cid=mm6645a1_w Accessed November 24, 2020
3.https://www.cdc.gov/nutritionreport/pdf/Nutrition_Book_complete508_final.pdf

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Prevalence of Vitamin C Deficiency and Low Vitamin C Concentration in US Population

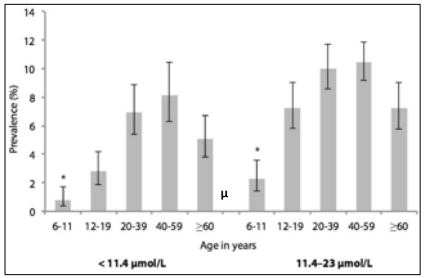

Figure H.1.f. Prevalence estimates of vitamin C deficiency (serum concentrations less than 11.4 µmol/L) and low vitamin C concentrations (11.4-23 µmol/L) in the U.S. population aged 6 years and older by age group, National Health & Nutrition Examination Survey, 2003-2006.

Error bars represent 95% of confidence intervals. *Prevalence in children is significantly lower than prevalence in persons 20 years and older (p <0.05).

NOTE: ***scurvy induced*** when dietary vitamin C intake < 10 mg/d and/or plasma vitamin C levels ***below 11 µmol/L***

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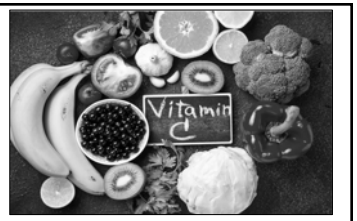
Vitamin C: *Acute Infection*



- ***Infection* depletes levels** due to increased inflammation and metabolism.
  - **35%** Scottish elders **hospitalized for acute respiratory infections: levels < 11 µmol/L.**[1]
  - **Canadian hospital: 19% patients had levels < 11 µmol/L**[1]
  - Paris hospital: **44% patients had levels < 6 µmol/L.**[1]
- Maintain adequate vitamin C levels, especially during periods of stress.

1. Hemila H, et al. Vitamin C Can Shorten the Length of Stay in the ICU: A Meta-Analysis. *Nutrients* 2019 Apr; 11(4): 708.

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"Picky" Eater?

- **Healthy 4-year-old boy** seen by ortho/rheumatology with **right-leg pain and progressively worse limping**, became **unable to weight bear.**
- Intermittent **non-blanching rash arms and legs** past 2 years, topical emollients not effective. **Bleeding when brushing teeth, gingivitis**.
- **Diet** primarily **waffles, yogurt, pasta with butter, goldfish crackers, peanut butter, chicken nuggets, and water.**
- Workup negative **except for *iron, vitamins C and D deficiencies*.**
- **100 mg ascorbic acid q 8 hours** x 7 days, then 1 x daily with **iron and vitamin D.**
- **Limp and rash completely disappeared within weeks.**

Nastro A, et al. Scurvy Due to Selective Diet in a Seemingly Healthy 4-Year-Old Boy. *Pediatrics* September 2019; 144 (3) e20182824.

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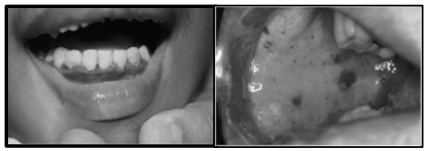
Vitamin C



- Deficiency increases risk for **periodontitis and xerostomia**. **Inflammation of gingiva followed by bleeding, ulceration, bad breath, followed by loss of bone and loosening of teeth.**
- Skin changes, **easy bruising, slow healing wounds, dry mouth, dry eyes. Emotionally labile. Weakened capillaries.** Hemorrhage is hallmark of scurvy and hair follicles are common site of cutaneous bleeding.
- Low ascorbic acid levels found in **healthy subjects with gingivitis** and in **diabetics with periodontitis**. 250 mg BID improved symptoms.[1]

1. Gokhale NH et al. *J Diet Suppl.* 2013;10:93–104.

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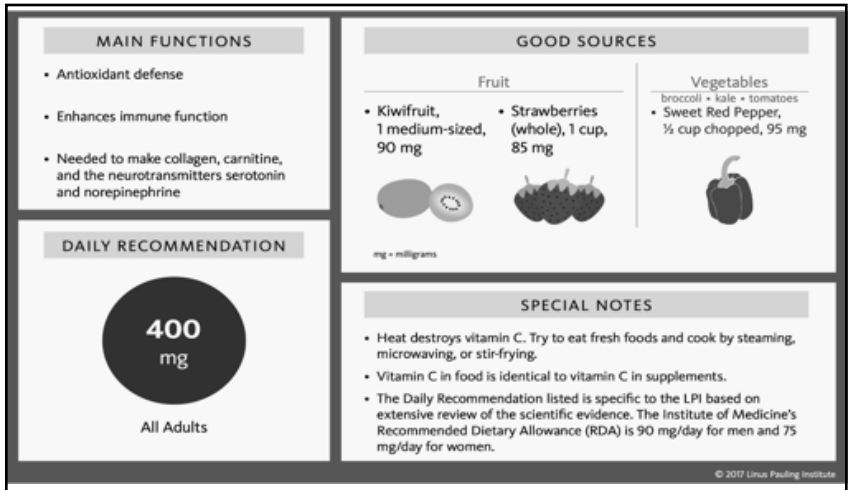

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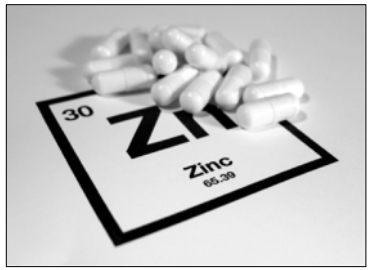
Zinc

- **"Gatekeeper"** of immune system.
- Improves **mucociliary clearance**, strengthens **epithelial integrity**, regulating **tight junction** proteins important for **mucosal membranes,** direct antibacterial effects against *S. pneumoniae*[1] and preserves antiviral immunity.
- Zinc deficiency/inadequacy affects **30%** of global population; responsible for **~800,000 deaths (e.g., diarrhea, pneumonia).**[2]
- **30–40% American *adults over 60 years are estimated to be zinc deficient.***



1. *Ejikeluamp BA, et al. PLOS Pathogens*, 2019; 15 (8): e1007
2. Wu, D, et al. *Front Immunol* 2019;. doi: 10.3389/fimmu.2018.03160
3. Hennigar SR, et al. *The Journal of Nutrition* 2018; 148(8): 1341-51

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Zinc & Immune Health

- Suboptimal zinc levels **increase risk for infectious diseases. Mild zinc deficiency is largely sub-clinical**, unnoticed in most people.
- Study 420 **nursing home patients: 29% zinc deficient even after one-year taking MVI with 7 mg zinc.**
- **Those with serum levels > 70 µg/dL** had **lower incidence of pneumonia, shorter duration of illness, less total antibiotic use.**

Meydani SN, et al. Serum zinc and pneumonia in nursing home elderly. *Am J Clin Nutr* 2007; 86, 1167–1173

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Zinc & Elders

- 53 nursing home residents tested: 31 (**58%) had low serum zinc levels** (<70 µg/dL).
- 31 elders randomized to **30 mg zinc/d** or **5 mg zinc/d** for **3 months.**
- **30 mg/d** group increased zinc levels **~16%;** many **did not reach** zinc levels > 70 µg/dL.
- The **increase** in serum zinc concentration **was associated with an increase in the number of T cells (P < 0.05).**

Barnett JB, et al. *Am J Clin Nutr* 2016 Mar;103(3):942-51.

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Zinc & COVID

- Prospective study of fasting zinc levels in **COVID-19 patients** at time of **hospitalization** found significantly **lower serum zinc levels** than controls ($p < 0.001$), with **57.4% being zinc deficient.**
- Odds of severe complications were **five-fold greater** in those who were zinc deficient.
- Higher rates of **complications** ($p = 0.009$), **acute respiratory distress syndrome** (18.5% vs 0%, $p = 0.06$), **prolonged hospital stays** ($p = 0.05$), and **increased mortality** (18.5% vs 0%, $p = 0.06$).

Jothimani D, et al. COVID-19: Poor outcomes in patients with zinc deficiency. *Int J Infect Dis* 2020 Nov;100:343-349.

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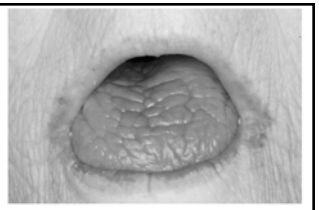
Zinc Deficiency



- Increased risk: vegans, alcoholics, those with HIV, cystic fibrosis, and inflammatory bowel disease; those taking statins/blood pressure meds.
- **Perioral and periorificial eczematous to pustular dermatitis in** *horseshoe-shaped configuration due to sparing of the upper lip.* **Angular cheilitis** with **oral ulcerations** may be present. Intraoral findings may include **flattening of the filiform papillae**, **impaired healing**, and sensations of **hypogeusia and xerostomia**.
- Deficiency: rough skin, hypogonadism/low sperm count, cognitive impairment, imbalanced immune reactions favoring allergies and autoimmune diseases

Perioral dermatitis associated with zinc deficiency. Photo by Dr. Mark Pittelkow, Mayo Clinic Department of Dermatology as published in: DiBaise M, et al. *Nutrition in Clinical Practice* 2019: 34(4): 490-503

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Zinc Deficiency

- **Elders, men** > women, **obese** individuals, patients with **diabetes and other chronic diseases** are all at risk **of zinc deficiency.**[1]
- Widely used **antihypertensive** drugs and statins negatively affect zinc status.[1]
- "*Preventive supplementation of subjects from risk groups should begin now, as zinc is a cost-efficient, globally available and simple to use option with little to no side effects.*"[2]
- RDA for **adult males 11 mg/d and 8 mg/d women**
- **15-30 mg/d zinc acetate, citrate, picolinate, or gluconate** for adults
- **Excessive zinc intake** can be toxic (>150 mg/d). **Safe UL set at 40 mg/d.**

1. Mossink JP. *BMJ Nutr Prev Health* 2020 Jun 17;3(1):111-117. 2. Wessels I, et al. *Front Immun* 2020; 11: 1712.

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Vitamin D

- Deficiency common globally but more **severe in elders** due to environmental/biological factors.
- **75% of elders** in nursing homes **severely** vitamin D **deficient** (25(OH)D < 10 ng/mL).
- **Obesity, dark skin**, living **northern latitudes**, use of **sunscreen**, all increase **deficiency risk**.
- Vitamin D increases **innate immunity** via secretion of **antiviral peptides**, strengthening **mucosal defenses** and **reducing risk of respiratory infections.**

Lips P, et al. *Eur J Endocrinol.* 2019;180:23–54.
Ali N. *J Infect Public Health* 2020; Oct; 13(10): 1373–1380.

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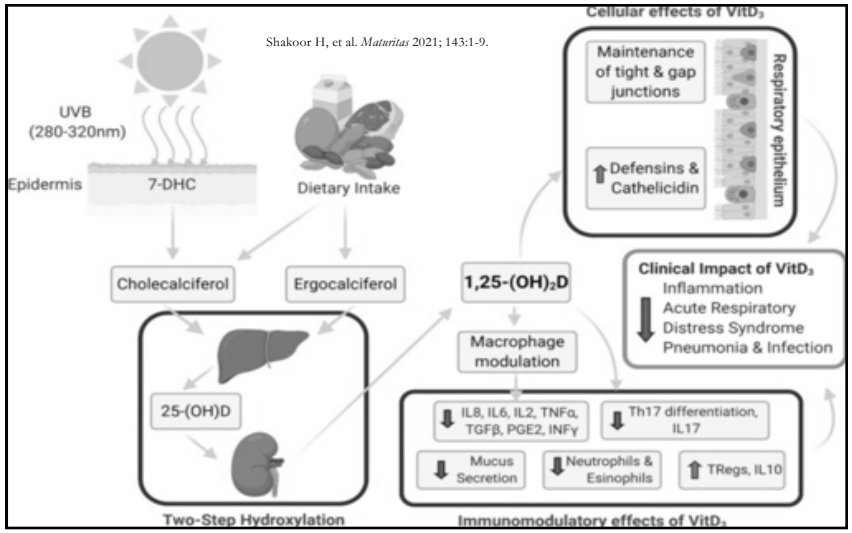

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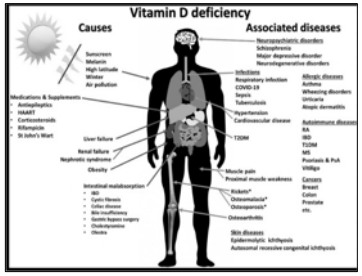
Vitamin D & Microbiome



- Vitamin D **ensures appropriate level of antimicrobial peptides in mucus; maintains intestinal barrier function**.
- If **bacteria penetrate** epithelial layer and enter interstitium, immune cells trigger adaptive immune response by activating Th1/Th17 cells. ***Vitamin D/VDR signaling in these cells ensures clearance of the bacteria.***

Fakhoury HMA, et al. *J Steroid Biochem Mol Biol* 2020

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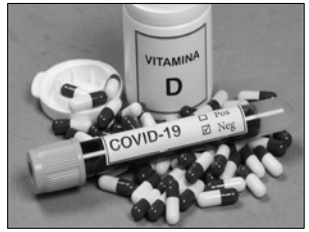
Vitamin D & Respiratory Infection

Martineau AR, et al. Vitamin D supplementation to prevent acute respiratory tract infections: systematic review and meta-analysis of individual participant data. *BMJ* 2017; 356: i6583.

- Acute respiratory infection kills **~2.65 million people/year.**
- Vitamin D releases antimicrobial peptides in the lungs, helps to mount immune response.
- **25 eligible randomized controlled trials (n=10,933, aged 0–95 years).**
- Supplementation **reduced risk of acute respiratory infection** among all participants (NNT=33) and **those who were vitamin D deficient experienced the most benefit (NNT=4).**

Vitamin D & COVID

- 212 cases COVID-19: **vitamin D deficient patients had 19.6-fold higher risk of critical** outcome compared to those with sufficient levels ($p < 0.001$).[1]
- Retrospective study: **780 confirmed cases SARS-CoV-2** infection found those vitamin D deficient ~**13 times more likely to die.**[2]
- Israeli data: **26% of COVID** patients **died** if vitamin D deficient soon before hospitalization, compared to 3% who had normal levels of vitamin D.
- Hospitalized patients **who were vitamin D deficient 14 times more likely to end up in severe or critical condition than others**.[3]



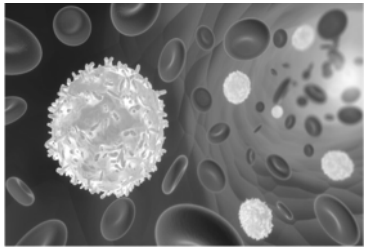
1. Alipio, M. Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-2019). *SSRN Electron. J.* 2020, doi:10.2139/ssrn.3571484;
2. Raharusun P., et al. Patterns of COVID-19 Mortality and Vitamin D: An Indonesian Study. *SSRN.* 2020 doi: 10.2139/ssrn.3585561
3. https://www.timesofisrael.com/1-in-4-hospitalized-covid-patients-who-lack-vitamin-d-die-israeli-study/

Vitamin D Deficiency

- **Serum 25(OH)D level** is used to determine vitamin D status. According to the American Endocrine Society:
  - Preferable level **40–60 ng/mL** (100–150 nmol/L)
  - **Sufficiency is 30 ng/mL** (75 nmol/L) and above
  - **Insufficiency** defined as **20-29 ng/mL**
  - **Deficiency** defined as **<20 ng/mL** (<50 nmol/L)
  - **Severe deficiency <12 ng/mL** (<30 nmol/L)
- **66.8 million Americans** 1 year and older levels between **12–20 ng/ml**
- **23 million Americans** 1 year and older: levels **less than 12 ng/ml**
  - Most at risk were *women and non-Hispanic blacks*.
- **2000–4000 IU per day appears necessary to maintain sufficient levels**.

CDC 2nd *National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population*
Holick MF, et al. *J Clin Endocrinol Metab* 2011; 96(7):1911-30

Vitamins B6



Cheng CH, et al. Vitamin B6 supplementation increases immune responses in critically ill patients. *Eur J Clin Nutr* 2006;60:1207–1213.

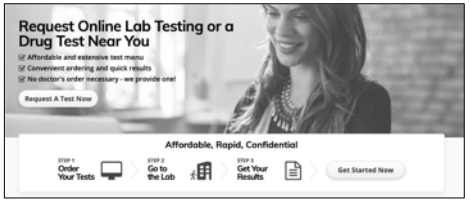
- **Folate and vitamins B6 and B12** all necessary for **production of white blood cells, crucial for immune health.**
- **Low vitamin B_6** significantly associated with **impaired humoral and cell-mediated immunity**; and increased **inflammation.**
- **Supplementing critically ill patients with B6 increases immune response.**
- **30 million Americans deficient in B6** (deficiency increases with age, higher in non-Hispanics, women on oral contraceptives, and those with inflammatory disorders).

My Recommendations

- Look for a ***multivitamin*** to provide key nutrients on daily basis.
  - **Vitamin A:** 2000–5000 IU per day (as retinol and/or beta carotene)
  - **Vitamin C:** 250–500 mg per day
  - **Zinc:** 10–20 mg per day
- **Test for vitamin D** and **correct any deficiency**. If testing is not done, supplement **2000–4000 IU** vitamin D3 per day with **fatty meal.**
- **If 65 and older and/or have risk factors for infection:**
  - **Zinc:** 30–40 mg per day
  - **Vitamin D3:** 4000 IU per day
  - **Vitamin C:** 500 mg 2–3 per day
  - **Zinc lozenges:** take 5–10 mg every every 2–3 hours at first sign of illness.

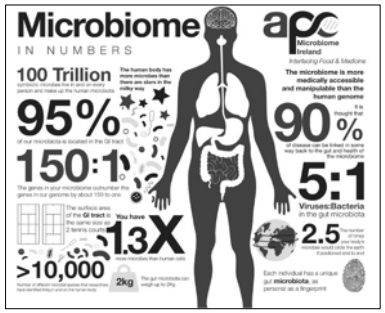
Where Can You Get Tested?

- Talk to your health care practitioner about potential concerns around micronutrient deficiencies.
- Most lab tests are readily available through LabCorp or Quest.
- If you want to order your own tests, I recommend www.requestatest.com.
- Vibrant America, EveryWell, and SpectraCell are also commonly used.



Definitions

- ***Microbiome***—collective **genomes** of microorganisms in particular environment.
- ***Microbiota***—community of **microorganisms** themselves.
- **Lower diversity** is marker of ***dysbiosis* (microbial imbalance),** which is associated with autoimmune disease, obesity, metabolic disorders, mental health, infection, and oral health.



Valdes AM, et al. *BMJ 2018;361:k2179*

Diet and the Microbiome

- **High-fiber plant-rich diet (**e.g., fruits, vegetables, whole grains, and legumes) supports growth and maintenance of **beneficial microbes**.
- **Probiotic foods** contain **live helpful bacteria**, and **prebiotic foods** contain **fiber and oligosaccharides** that **feed and maintain healthy colonies of those bacteria.**
- **Probiotic foods:** kefir, yogurt with live active cultures, fermented vegetables, sauerkraut, tempeh, kombucha tea, kimchi, and miso.
- **Prebiotic foods:** garlic, onions, leeks, asparagus, Jerusalem artichokes, dandelion greens, bananas and seaweed.

Fruits	Serving size	Total fiber (grams)*
Raspberries	1 cup	8.0
Pear	1 medium	5.5
Apple, with skin	1 medium	4.5
Banana	1 medium	3.0
Orange	1 medium	3.0
Strawberries	1 cup	3.0

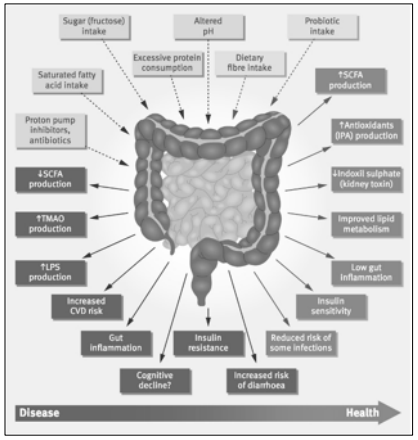
Vegetables	Serving size	Total fiber (grams)*
Green peas, boiled	1 cup	9.0
Broccoli, boiled	1 cup chopped	5.0
Turnip greens, boiled	1 cup	5.0
Brussels sprouts, boiled	1 cup	4.0
Potato, with skin, baked	1 medium	4.0
Sweet corn, boiled	1 cup	3.5
Cauliflower, raw	1 cup chopped	2.0
Carrot, raw	1 medium	1.5

https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/high-fiber-foods/art-20050948

Grains	Serving size	Total fiber (grams)*
Spaghetti, whole-wheat, cooked	1 cup	6.0
Barley, pearled, cooked	1 cup	6.0
Bran flakes	3/4 cup	5.5
Quinoa, cooked	1 cup	5.0
Oat bran muffin	1 medium	5.0
Oatmeal, instant, cooked	1 cup	5.0
Popcorn, air-popped	3 cups	3.5
Brown rice, cooked	1 cup	3.5
Bread, whole-wheat	1 slice	2.0

Legumes, nuts and seeds	Serving size	Total fiber (grams)*
Split peas, boiled	1 cup	16.0
Lentils, boiled	1 cup	15.5
Black beans, boiled	1 cup	15.0
Baked beans, canned	1 cup	10.0
Chia seeds	1 ounce	10.0
Almonds	1 ounce (23 nuts)	3.5
Pistachios	1 ounce (49 nuts)	3.0
Sunflower kernels	1 ounce	3.0

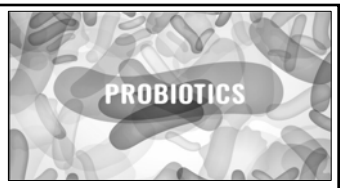
https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/high-fiber-foods/art-20050948



Diet, lifestyle, and medications can **dramatically impact** the microbiome and ultimately impact human health.

From: Valdes AM, et al. Role of gut microbiota in nutrition and health. *British Medical Journal* 2018;361:j2179

Probiotics



- **Live microorganisms** administered in adequate amounts confer *health benefit to the host.*
- Regulate/modulate immune functions, **reduce risk intestinal infection.**
- Improve **intestinal barrier functions, reduce endotoxemia.**
- Induce hypo-responsiveness to **food antigens.**
- Improve **glucose control** and **reduce inflammatory cytokines.**
- Inhibit tumorigenesis and **may inhibit cancer progression.**

Gianotti L. et al. *World J Gastroenterol.* 2010;16:167–175

Szulinska M, et al. *Nutrients* 2018, *10*(6), 773; https://doi.org/10.3390/nu10060773

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AEProbio — Clinical Guide to Probiotic Products Available in USA

Applications, Dosage Forms and Clinical Evidence to Date - 2022 Edition

Introduction | Adult Health | Womens Health | Pediatric Health | Functional Foods | References | About

PROBIOTIC APPLICATIONS IN ADULT HEALTH

Show 30 entries

Brand Name	Probiotic Strain	Applications (Level of Recommendation)	Dosage Form	CFU/Dose	No of Doses/Day
DanActive Actimel®	L. casei sp. Paracasei CNCM I-1518	AAD - Antibiotic associated diarrhea - Prevention (I) CID - Common infectious disease - community acquired (I)	Ferm. milk lq.	10B/serving	1-2 servings
UltraFlora® Immune Booster	L.plantarum HEAL9 L. paracasei 8700:2	CID - Common infectious disease - community acquired (I)	Capsule	1B/capsule	1 capsule
Yakult	L.casei Shirota	C - Constipation (I) CID - Common infectious disease - community acquired (I) M/A - Mood and Affect (symptoms related to stress/anxiety; not a substitute for standard treatment) (III)	Bottle	6B/bottle (80ml)	1-2 bottles
FlorastorMax®	Saccharomyces boulardii lyo CNCM I-745	AAD - Antibiotic associated diarrhea - Prevention (I) CDAD - Clostridium difficile associated diarrhea - Prevention (I) HP - Helicobacter pylori - Adjunct to standard eradication therapy (I) IBD-UC - IBD - Ulcerative colitis - Adjunct to standard therapy (III) TD - Traveler's diarrhea prevention (I)	Sachet	10B/sachet	1 sachet
Florastor®	Saccharomyces boulardii lyo CNCM I-745	AAD - Antibiotic associated diarrhea - Prevention (I) CDAD - Clostridium difficile associated diarrhea - Prevention (I) HP - Helicobacter pylori - Adjunct to standard eradication therapy (I)	Sachet Capsule	5B/sachet 5B/capsule	1-2 sachets 1-2 capsules
Bio-K+® BiomePRO®+	L. acidophilus CL1285 L. casei LBC80R L. rhamnosus CLR2	AAD - Antibiotic associated diarrhea - Prevention (I) CDAD - Clostridium difficile associated diarrhea - Prevention (I) IBS - Irritable bowel syndrome (I)	Capsule	50B/capsule	1-2 capsules
Bio-K+® BiomePRO Drinkable Probiotic®	L. acidophilus CL1285 L. casei LBC80R L. rhamnosus CLR2	AAD - Antibiotic associated diarrhea - Prevention (I) CDAD - Clostridium difficile associated diarrhea - Prevention (I)	Ferm. rice lq.	100B/bottle	0.5-1 bottle
Bio-K+® Drinkable Probiotics®	L. acidophilus CL1285 L. casei LBC80R L. rhamnosus CLR2	AAD - Antibiotic associated diarrhea - Prevention (I) CDAD - Clostridium difficile associated diarrhea - Prevention (I)	Ferm. vegan. lq. Ferm. milk lq.	50B/bottle 50B/bottle	1 bottle 1 bottle
CulturelleⓇ Digestive Health Daily Probiotic	L. rhamnosus GG	AAD - Antibiotic associated diarrhea - Prevention (I) CDAD - Clostridium difficile associated diarrhea - Prevention (III) HP - Helicobacter pylori - Adjunct to standard eradication therapy (I) IBD-P - Inflammatory bowel disease - Pouchitis (II) TD - Traveler's diarrhea prevention (II)	Capsule Chewable tablet	10B/capsule 10B/tablet	1 capsule 1 tablet

http://www.usprobioticguide.com/PBCAdultHealth.html?utm_source=adult_ind&utm_medium=civ&utm_campaign=USA_CHART Accessed May 10, 2022

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Prevention Cold and Flu-Like Symptoms

- **DBPCT 326 children** (3–5 years age) randomized to placebo (N = 104), *L. acidophilus* NCFM (N = 110), or *L. acidophilus* NCFM + *Bifidobacterium lactis* Bi-07 (N = 112). Children treated 2 x daily for 6 months.
- **Compared to placebo:**
  - Single and combination probiotics reduced ***incidence*** of **fever** 53% (P = .0085) and 72.7% (P = .0009), **coughing** 41.4% (P = .027) and 62.1% (P = .005), **rhinorrhea** 28.2% (P = .68) and 58.9% (P = .03), respectively.
  - **Fever, coughing, and rhinorrhea *duration*** decreased significantly by 32% (single strain; P = .0023) and 48% (combination; P < .001).
  - ***Antibiotic use incidence*** reduced 68.4% (single; P = .0002) and 84.3% (combination; P < .0001).

Leyer GJ, et al. Probiotic effects on cold and influenza-like symptom incidence and duration in children. *Pediatrics* 2009 Aug;124(2):e172-9.

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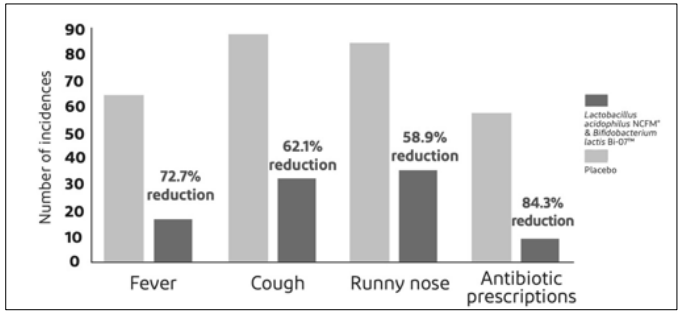
Reduction in Symptoms, Antibiotic Use with *L. acidophilus* NCFM + *B. lactis* Bi-07



Leyer, GJ, et al. Probiotic effects on cold and influenza-like symptom incidence and duration in children. *Pediatrics* 2009; 124(2): e172-179.

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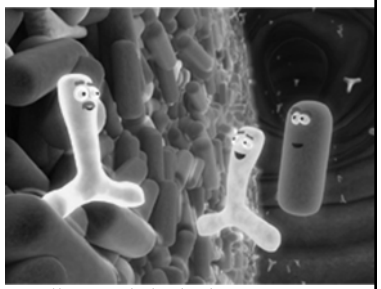
Acute Infectious Diarrhea

- **High quality evidence support** probiotics in **acute infectious diarrhea**, common for those **traveling,** kids going to **daycare,** etc.
  - Start probiotics first sign of diarrhea + 2 weeks beyond; start 2 days before travel + trip duration.
- Meta-analysis **17 RCTs** (2,102 children): significant **reduction in duration** of diarrhea with *S. boulardii* (20 fewer hours).[2]
- Meta-analysis **8 RCTs** (1,229 children): *L. reuteri* DSM 17938 reduced duration of diarrhea (25 fewer hours), increased cure rate on days 1 and 2.[3]



1. https://www.aafp.org/afp/2017/0801/p170.html. Accessed December 22, 2020
2. Feizizadeh S, et al. Efficacy and safety of *Saccharomyces boulardii* for acute diarrhea. *Pediatrics.* 2014;134(1):e176–e191.
3. Urbańska M, et al. Systematic review with meta-analysis: *Lactobacillus reuteri* DSM 17938 for diarrhoeal diseases in children. *Aliment Pharmacol Ther.* 2016;43(10):1025–1034.

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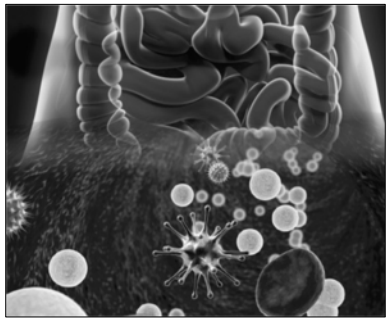
Proton Pump Inhibitors: GI Infection

- ***PPIs disrupt microbiota.***
- Meta-analysis 23 studies (n=300,000): ***65% increased risk C. difficile*** associated diarrhea. (CDC lists C. diff "**urgent threat**").[1]
- PPI users ***5 times risk* of developing GI infections** compared to non-users.[2]
- Significant association **between acid-suppressive therapies and risk of *C. difficile* and pneumonia in children.**[3]



Janarthanan S, et al. *Am J Gastroenterol* 2012;107:1001–10
2. Hafiz RA, et al. *Ann Pharmacother.* 2018 Jul;52(7):613-622.
3. De Bruyne P, et al. *Arch Dis Child* 2018; 103(1):78-82

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PPI + Probiotics *in Children*

- 128 children with GERD randomized to **12 weeks PPI** (esomeprazole 1 mg/kg/d; max 40 mg) **plus probiotics** (*Lactobacillus reuteri* DM 17938) or identical **placebo**. Control: 120 healthy age-matched children.
- After 12 weeks, **dysbiosis** occurred in **56.2% of group** receiving **placebo *versus* 6.2%** of those taking **probiotics (p<0.001).**
- **Probiotics + PPI** significantly **decreased prevalence of SIBO** among children with GERD compared to PPI and placebo ($P < 0.001$).

Belei O, et al. *J Neurogastroenterol Motil.* 2018 Jan 30;24(1):51-57.

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PPIs and the Immune System

- **PPIs are risk factor** for **rotavirus**, **influenza**, **norovirus**, and **Middle East respiratory syndrome coronavirus** infections; **increased risk of acute gastroenteritis** during periods of highest circulation of enteric viruses.[1]
- Review by Cedars-Sinai (53,130 people): once daily dosing conferred **215% increased risk positive COVID** test, twice daily dosing **367% increased risk.**
- Study in Korea found 79% **greater risk of severe COVID** if taking PPI.[3]

1. Charpiat B, et al. Proton Pump Inhibitors are Risk Factors for Viral Infections: Even for COVID-19? *Clin Drug Investig* 2020 Oct;40(10):897-899.
2. Almario CV, et al. Increased Risk of COVID-19 Among Users of Proton Pump Inhibitors. *Am J Gastroenterol* 2020 Oct;115(10):1707-1715.
3. Lee SW, et al. Severe clinical outcomes of COVID-19 associated with proton pump inhibitors: a nationwide cohort study with propensity score matching. *Gut* 2021 Jan;70(1):76-84.

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Outcome	Reference	No of studies/ participants	Evidence of benefit?
Clostridium difficile associated diarrhoea in adults and children	Goldenberg et al (2017)[111]	39/9955	Yes
Necrotising enterocolitis	Al Faleh et al (2014)[112] Rees et al (2017)[113]	17/5338	Yes
Antibiotic associated diarrhoea in children	Goldenberg et al (2015)[114]	26/3898	Yes
Probiotics for preventing acute upper respiratory tract infections	Hao et al (2015)[115]	12/3720	Yes
Urinary tract infections	Schwenger et al (2015)[116]	9/735	No
Prevention of asthma and wheeze in infants	Azad et al (2013)[117]	6/1364	No
Prevention of eczema in infants and children	Mansfield et al (2014)	16/2797	Yes
Prevention of invasive fungal infections in preterm neonates	Agrawal et al (2015)[119]	19/4912	Unclear
Prevention of nosocomial infections	Manzanares et al (2015)[120]	30/2972	Yes
Treatment of rotavirus diarrhoea in infants and children	Ahmadi et al (2015)[121]	14/1149	Yes
Prevention and treatment of Crohn's disease and ulcerative colitis	Saez Lara et al (2015)[122]	14/821 ulcerative colitis 8/374 Crohn's disease	Yes
Pulmonary exacerbations in children with cystic fibrosis	Ananthan et al (2016)[123]	9/275	Yes
Type 2 diabetes (fasting glucose, glycated haemoglobin test)	Akbari et al (2016)[124]	13/805	Yes
Type 2 diabetes (insulin resistance, insulin levels)	Zhang et al (2016)[125]	7/425	Yes
Necrotising enterocolitis in pre-term neonates with focus on *Lactobacillus reuteri*	Athalye-Jape et al (2016)[126]	6/1778	Yes
Reduction of serum concentration of C reactive protein	Mazidi et al (2017)[127]	19/935	Yes
Cardiovascular risk factors in patients with type 2 diabetes	Hendijani et al (2017)[128]	11/641	Yes
Reduction of total cholesterol and low density lipoprotein cholesterol	Wu et al (2017)[129]	15/976	Yes
Depressive symptoms	Wallace and Milev (2017)[78,130]	6/1080	Yes
Vulvovaginal candidiasis in non-pregnant women	Xie et al (2018)[131]	10/1656	Yes

From: Valdes AM, et al. Role of gut microbiota in nutrition and health. *BMJ* 2018;361:j2179

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http://herbalgram.org/resources/herbalegram/volumes/volume-18/volume-18-issue-1-january-2021/thailand-approves-asian-herb-andrographis-to-treat-covid-19/thailand-approves-asian-herb-andrographis-to-treat-covid-19/

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Acute Respiratory Tract Infections

- **2017 systematic review** (33 RCT, N = 7,175) found **andrographis improved cough, sore throat and overall symptoms compared to placebo and other herbal treatments.**
- **12 studies meta-analysis** comparing andrographis to **usual care** (analgesics, antibiotics, anti-inflammatories, antivirals, corticosteroids, or steroids) indicated a **statistically significant reduction in sore throat and sick leave.**
- **AE ~10%, most common nonserious GI.**

Hu XY, et al. *PLoS One.* 2017;12(8): doi: 10.1371/journal.pone.0181780
Worakunphanich W, et al. *Pharmacoepidemiol Drug Saf* 2021;30(6):727-739.

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Elder Flower/Berry (*Sambucus nigra*)

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Table 3. Human clinical studies on the effects of various *Sambucus nigra* treatments against influenza

Study	Treatment	dosage	*n*	Results	*p*
Zakay-Rones *et al.*, 1995	Sambucol®	4 tsp (all adults) once daily for 2 days	25	Absence of side-effects in healthy adults	
		4 tsp (adults) or 2 tsp (children) once daily for 2 days	27	Recovery from fever in 4 days instead of 6 or more days	<0.01
				Symptomatic improvement in 2 days instead of 5 or more days	<0.001
				Complete recovery in 2–3 days instead of 5 or more days	<0.001
Konlee, 1998	Sambucol®			Lessened duration of illness	
Zakay-Rones *et al.*, 2004	Sambucol®	15 mL four times daily for 5 days	60	All individual symptoms relieved in 2–4 days instead of 7–8 days	<0.001
				Global assessment showed pronounced improvement after 3 days instead of 7 days	<0.001
				Less use of rescue medication than control	<0.001
				Absence of side-effects in patients	
Kong, 2009	Elderberry extract lozenge from HerbalScience Singapore Pte. Ltd.	4 lozenges daily for 2 days	64	24 h: significant improvement in all symptoms except coughing and mucus discharge	<0.0001
				48 h: significant improvement in all symptoms	<0.0001
				48 h: complete eradication of all symptoms in 28% of treatment group and 0% of control group	
				Absence of side effects in patients	
Tiralongo *et al.*, 2016	Rubini capsules	2 capsules/day priming (9 days), then 3 capsules/day (6 days)	29	Lessened symptom severity	0.05
				Lessened illness duration	0.02
				No significant difference in use of rescue medications	0.9
			312	Less occurrence of illness in treatment group (not significant)	0.2

All studies were randomized, double-blinded, and placebo-controlled, with acceptable patient compliance.

Phytother. Res. **31:** 533–554 (2017)

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Echinacea and Elderberry

- 473 patients with flu symptoms less than 48 hours randomized to **240 mg echinacea herb/root extract + elderberry** fruit (Vogel Bioforce) or **tamiflu.**
- **No difference between recovery rates,** antibiotic use, intermediate doctor visits, use of over-the-counter medications for symptoms, "ability to return to normal daily activities," or physician- and patient-reported efficacy of the treatments.
- Safety positive.

Rauš K, et al. *Curr Ther Res.* 2015 Dec; 77: 66–72.

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Negative Trial

- 87 patients, over age four, **with < 48 h of at least 2 moderate-severity influenza** symptoms and **positive PCR influenza test.**
- Patients 5-12 years received placebo or **15 ml (5.7 g) elderberry extract twice a day for 5 days; those > 12 years received 15 ml 4 times a day for 5 days.**
- Average number of days to **complete resolution was 8.7 ± 3.8 and 8.6 ± 3.9 in the placebo and elderberry group, respectively (p = 0.87).**
- No benefit seen in this clinical trial.

Mackinn M, et al. Elderberry Extract Outpatient Influenza Treatment for Emergency Room Patients Ages 5 and Above: a Randomized, Double-Blind, Placebo-Controlled Trial. *J Gen Intern Med* 2020 Nov;35(11):3271-3277.

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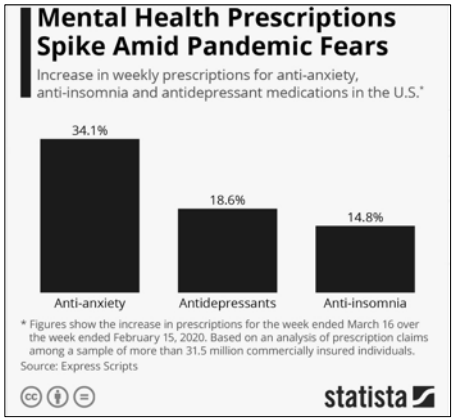

Increased use of anxiolytics, antidepressants, and sleeping agents, during this pandemic, started early and has shown little signs of slowing.

Chronic Stress and the Immune System

- Can lead to **anxiety, depression, insomnia, weakened immune system.**
- Leads to **persistently high glucocorticoid** (e.g., cortisol) **levels,** which can **lead to dysregulation** of both **innate and adaptive immune responses.**
- Stress in **childhood** may **impact immune system in adulthood.**
- Chronic stress influences **altered immune response in elders**.
- **Non-restorative sleep weakens immune system.**

Epel ES, Lithgow GJ. Stress biology and aging mechanisms: toward understanding the deep connection between adaptation to stress and longevity. *J Gerontol A Biol Sci Med Sci.* 2014;69(Suppl 1):S10–6; Kuang XD, et al.. *Biomed Envi Sci.* 2018,31(9):686-699; UCSF Center on Disparities on Health

Immune Health is *in Our Hands*

- Frequent **handwashing** with soap and water.
- **Plant-**rich, **high-fiber** diet with adequate protein. **Limit added sugars**.
- Support natural **"barriers"** (skin, nasal passages, lungs, GI tract).
- Correct **micronutrient deficiencies**. Multivitamin wise.
- Clinically tested **probiotic strains** for immune support, particularly during cold and flu season, and/or children taking antibiotics/PPIs.
- **Water as *primary beverage*** of hydration, drink herbal teas.
- **Ensure regular restorative rest and sleep**.
- Create healthy stress management plan, get regular exercise.