Welcome!

• We are about to take a journey into one of the most amazing 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 much much more.
• As with any educational program…. Please make sure you use the information wisely. Keep current on CDC and state guidelines that impact your clinical practice and family health.

Innate Immune Response

• Innate immunity: first line of defense, immediate and nonspecific. Lack of immunologic memory means same response is mounted regardless of how often a specific invader is encountered.
• Anatomical barriers
  • The skin is a strong physical barrier
  • Sweat and tears contain lysozymes that inhibit bacterial growth
  • Cilia in nose and lungs trap microbes
  • Cough and sneezing removes them
  • Stomach acid destroys many microbes
  • Microbiota compete for space/nutrients
  • Cross talk between intestinal microbiota and immune cells

Innate Immunity

• Soluble Factors: important for recruiting phagocytes to site of infection
  • Complement: network of > 30 proteins on cell surfaces and in plasma
    • Can directly kill pathogens, or activate phagocytosis
    • Regulate inflammatory response
  • Cytokines: chemical messengers with numerous roles: involved in inflammation, some directly fight pathogens, interferons have antiviral activity.
  • Phagocytes: engulf and digest pathogens, stimulate inflammatory cytokines
    • Monocytes, macrophages and neutrophils
Adaptive Immunity

• Second line of defense, takes days or weeks to fully 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

Fever

• Enhances immune function
• Increases activity of white blood cells
• Stimulates interferon and activates T-cells
• Interferes with growth/survival of microbes
• Increases heart and respiration rate
• Resets hypothalamus temperature control
• Temp lower in the morning, higher in the evening.
• Fever is considered a temperature higher than 100.4 F (38 C)

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 urination for 6 hours, no wet diaper 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.

Checkpoint: Sepsis

- Anyone can become septic. Diabetes, lung or kidney disease, cancer, increase the risk.
- Adults 65 or older
- People with weakened immune systems
- Children younger than one year old
- Most frequent organisms associated with sepsis include Staphylococcus aureus (staph) and Escherichia coli (E. coli).
- ~270,000 Americans die of sepsis every year


[Links to measles case data in Europe and US]
Immunizations

- 1900: top causes of death: pneumonia and flu, TB, and GI infections.
- Improvements in sanitation, maternal-infant care, public health (vaccinations), and medical treatments, such as antibiotics, led to dramatic declines in deaths from infectious diseases during 20th century.
- Ask your health care provider to discuss risks/benefits of immunizations for you and your family. CDC immunization schedule: https://www.cdc.gov/vaccines/index.htm

Recent Pandemics

- 1918-19 H1N1 “Spanish flu”: 500 million people infected; 50 million died globally; 675,000 people in US died. High death rate: 15-34 years age
- 1957-58 H2N2 virus: 1.1 million deaths globally; 116,000 US
- 1968-70 H3N2 (Hong Kong Flu): 1 million deaths globally; 100,000 in US, mostly in those > 65 years old. This virus continues to circulate
- 2009 H1N1 pdm09 virus: 1/3rd of people over the age of 60 had antibodies; 60.8 million cases globally and 12,469 deaths in US
- 2019-20 SARS-CoV2 Virus: 22,730,838 cases and 793,875 deaths globally; 5,718,582 cases and 176,768 deaths in US (as of 08/20/20)

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 410,000-740,000 hospitalizations and 24,000-62,000 deaths.

https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm
Severe Acute Respiratory Syndrome (SARS)

- **SARS** coronavirus first reported Asia February 2003: 8,098 people worldwide became sick; 774 died.
- **SARS-COV2** virus (COVID 19) new coronavirus has spread throughout world. Primarily spread person-to-person through respiratory droplets.
- Symptoms: fever, cough, shortness of breath, fatigue; less common, sore throat, headache, GI symptoms, loss of taste or smell
- Risk groups: age >65 years; obese individuals (BMI 30 roughly 50% hospitalized patients), blacks, certain Native American tribes, those with underlying health conditions (lung or heart disease, diabetes).


CDC: Antibiotic Resistance Threats in US, 2019

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

The Immune System

- We have been living with “germs” since the beginning – they predate us – they are what germinated life.
- However, with factory farms, viral/antibiotic resistance, increasing population density, human migration, eradication of predators, and damaged ecosystems.... pandemics will continue...... and we must think more broadly about how we will all move forward.
“When we try to pick out anything by itself, we find it hitched to everything else in the universe.”

John Muir

Antibiotics are used more heavily in farm animals than in people. This may be the largest source of antibiotic-resistant bacteria.

Drug resistance grows spread more widely and rapidly on farms than scientists even thought new discoveries show.

The agricultural industry says fears are exaggerated, whereas researchers say companies are endangering public health.

Regenerative agriculture can make farmers stewards of the land again.

Wolves keep Yellowstone in balance.
Prevention is In Your Hands
WASH them frequently

Lifestyle Matters

- **Diet** – rich in fruits, vegetables, protein and healthy fats. Make sure to cook meats thoroughly; use a separate cutting board for preparation.
- **Hydrate** – drink lots of water (also herbal teas, low sugar juices, etc.)
- **Weight** – maintain a healthy weight
- **Sleep** – ensure regular and restorative rest
- **Stress** – find healthy strategies for coping
- **Exercise** – regular physical activity

Diet and Immunity

- **Optimal immune response** requires adequate diet and nutrition to both prevent and recover from infection.
- **Poor nutrient status** is associated with inflammation and oxidative stress, which negatively impact the immune system.
- **Deficiencies of key dietary components** (e.g., protein, fiber, carotenoids, polyphenols; vitamins C, D, E; zinc) impair immune function.

Protein is Crucial

- Adequate protein intake is crucial for optimal antibody production.
- Low protein (below 0.8 g/kg bodyweight) can decrease active immunoglobulins and gut-associated lymphoid tissue (GALT), which play a role in gut-mucosal defense against infection.
- Protein malnutrition increases susceptibility to Zika and influenza viruses due to decreased bactericidal function of neutrophils, complement system, and IgA, as well as antibody response in humans.
- Low albumin and also low iron and vitamin E correlated with lower responses to influenza vaccination in the elderly.


Protein Choices

- Protein intake should be of high biological value and from healthy dietary choices: legumes, nuts, eggs, fish, lean meats (e.g., poultry), dairy, etc.

(Dietary Fiber

- Dietary fibers (mostly complex carbohydrates) key for healthy gut microbiota, intestinal barrier function and keeping inflammation in check.
- Significant reduction in hs-CRP concentrations observed 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.

Test for Inflammation

- Note: High sensitivity C-reactive protein (hs-CRP) is a protein produced by the liver which rises in response to inflammation.
- hs-CRP levels blood level between 1-3 milligrams/L often signals a low, yet chronic, level of inflammation.
- Do not test if you have recently been sick or have done highly strenuous exercise.

Garlic

Garlic and onions long used to treat respiratory and digestive infections (antibacterial, antifungal, antiviral)
- Rich in sulfur-containing compounds such as alliin, and allicin, and flavonoids such as quercetin.
- Garlic increases macrophage activity, NK cells, and production of T and B cells.
- Clinical trials show garlic significantly reduces the number, duration, and severity of upper respiratory infections.
- “Garlic supplements are well tolerated and may be considered as a complementary treatment option for hypertension, slightly elevated cholesterol, and stimulation of immunity.”

Vitamin C and Immunity

- Plays crucial role in innate and adaptive immune responses. Maintains epithelial barrier function.
- Increases antibodies and complement proteins
- Supplementation shortens duration and severity of upper respiratory tract infections, particularly those under stress.
- Deficiency common in critically ill patients due to increased needs and decreased intake.
- Need is higher that current RDA – most experts believe 200-400 mg per day is required. Acute dosing for those who are ill may be much higher.

For references, see the citations provided at the end of the text.
**Zinc**

- Involved in innate and adaptive immune response; reduces viral attachment and replication.
- In developing countries, zinc deficiency ~800,000 deaths (diarrhea, pneumonia).
- Inadequate zinc intake common in elders.
- 35–45% US adults > 60 years intake below EAR (estimated average requirement)

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**Zinc and Immunity**

- Studies in healthy elders and those with zinc deficiency show lower rates of respiratory infections, pneumonia, and antibiotic use with zinc supplements.
- 12-month study 420 nursing home patients: those with plasma concentrations >70 µg/dL had lower risk of pneumonia

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**Zinc and Immunity**

- Zinc lozenges significantly reduce duration of cold at a dose of up to ~80 mg/day for up to 10 days.
- Zinc shortens duration of diarrhea, particularly when combined with *Saccharomyces boulardii* or *L. rhamnosus GG,*
- Dose: 15-30 mg/d of zinc acetate, citrate, picolinate, or gluconate for adults.
- Do NOT exceed 50 mg per day for longer than 2-3 months without speaking with health care provider (risk of copper deficiency).
Vitamin D

• Sun and cod liver oil long used to treat TB
• Vitamin D receptor highly expressed in lungs, triggers production of cathelicidin & defensin, reducing risk of lung infection.
• Analysis 212 cases of COVID-19: those with vitamin D deficiency had 19.6-fold higher risk of critical outcome compared to those with sufficient levels (p < 0.001)


Vitamin D and Respiratory Infection

• Acute respiratory infection kills ~2.65 million people/year.
• 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 A

• Essential for both innate and adaptive immunity.
• Critical for formation and maintenance of healthy barrier function of the skin, lungs, and GI tract, necessary for enhancing antigen non-specific immunity functions
• 43 RCT: supplementation in developing nations reduced measles mortality by 50% in children.
• In US, 45% Americans do not meet the EAR. Need 700-900 mcg/d

Reider CA, et al. Nutrients 2020; 12, 17:35

Vitamins B6

• Folate and vitamins B6 and B12 all necessary for production of white blood cells, crucial for immune health.
• Low vitamin B6 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)


To Get JUST 1.5mg of B6 in Food

• 2.5 bananas OR
• 12 Tbsp roasted sunflower seeds OR
• 7-8 ounces chicken breast OR
• 7-8 ounces sockeye salmon OR
• ~5 ounces cooked tuna OR
• ~5 ounces beef liver OR
• 3.5 cups raw diced avocados OR
• 4.5 medium sweet potatoes, cooked, skin on OR
• 2.5 medium potatoes, cooked, with skin OR
• 15 cups of milk
Vitamin B12 Deficiency

- B12 deficient patients have decreased levels of CD8+ cells and subdued activity of NK cells.
- Institute of Medicine recommends adults > 50 yrs get B12 from fortified foods/supplements (2.4-5 mcg/d)
- Deficiency: tingling/numbness in hands and feet, fatigue, shortness of breath, loss of appetite, joint pain, depression, loss of taste and smell, cognitive impairment, and dementia.
- 2015 meta-analysis: 80% increased risk B12 deficiency after 10 months of regular PPI use.
- Meta analysis 29 studies: 245% increased risk B12 deficiency metformin use.


Microbiota........

- Train and modulate immune system (e.g., skin, gut)
- Convert skin oils to compounds that keep skin supple and lower pH
- Block adhesion and suppress growth of pathogenic bacteria
- Break down carbs and make β-hydroxybutyrate, energy for intestinal cells but also crucial for maintaining tight junctions to reduce permeability.
- Make ARA and DHA, signal brain cells to divide (infants). Gut and brain neurons communicate. Gut microbes make serotonin, melatonin, GABA, and others.
- Produce vitamins and assist in building amino acids.
- Help maintain blood pressure (complex carbs –formate –impact salt processing)

• Many dietary, lifestyle and medications can dramatically impact the microbiome and ultimately impact human health.
• Antibiotics and PPIs are major disruptors of gut microbiota.


• Antibiotics and PPIs are major disruptors of gut microbiota.


• High fructose diet increases intestinal permeability.
• Bacterial endotoxins (LPS) enter the bloodstream, inflammation is activated by changing insulin signaling and triggering inflammatory mediators, which impact immune health.

Jegatheesan P, et al. *Nutrients* 2017; Mar 3(9)

Microbes Need Fiber

• Fiber is main source of microbiota-accessible carb in human diet.
• Low-fiber diet in modern life, known as fiber gap, can trigger depletion of human gut microbiota diversity and beneficial metabolites.
• Short-chain fatty acids are one of major microbial metabolites of dietary fibers, which can improve intestinal mucosal immunity.


Probiotics and Respiratory Infection

• Probiotics >placebo in reducing number of acute upper respiratory tract infections (URTI) and reducing antibiotic use.1
• Meta-analysis 23 trials 6269 children (newborn – 18 years): probiotics reduced number of children having respiratory infections with fewer days of absence from school. Authors concluded, “Based on the available data and taking into account the safety profile of RCTs, probiotic consumption appears to be a feasible way to decrease the incidence of RTIs in children.”2

Acute Infectious Diarrhea

• **Strong evidence** for probiotics in **acute infectious diarrhea**, which is common for those traveling, kids going to daycare, etc.

• **Meta-analysis 17 RCTs** (2,102 children): significant **reduction in duration** of diarrhea with *S. boulardii* use (20 fewer hours).¹

• **Meta-analysis 8 RCTs** (1,229 children): *L. reuteri* reduced duration of diarrhea (25 fewer hours), increased cure rate on days 1 and 2.²

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Resource: www.usprobioticguide.com
Echinacea and Elderberry

• Hydroethanolic extract prepared from freshly harvested Echinacea purpurea has demonstrated strong activity against influenza virus strains (H1N1, H3N2, H5N1, H7N7, H1N1pdm2009)
• 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 from numerous trials is very positive.

**Things to Keep ON HAND**

- **Multivitamin** – this should provide you vitamin A, Bs, D, zinc, etc.
- **Vitamin D** – get your level checked – want ~35-50 ng/mL.
- Requestatetest.com or everlywell.com
- If not testing: 2000-4000 IU/d (50-100 mcg/d) vitamin D3
- **Zinc lozenges** - for acute needs (5-8 mg per lozenge)
- **Vitamin C** – keep 250-1000 mg tabs/powders/gummies available.
- **Probiotics** – mixed strain of Lactobacillus, Bifidobacteria, and/or Saccharomyces boulardii.
- **Thermometer** (appropriate for family)
- **Fever reliever** (acetaminophen, ibuprofen) appropriate for family

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**Chronic Psychological Stress**

*Mental/emotional strain where individual perceives demands tax or exceed their adaptive capacity.*

Chronic Stress and the Immune System

• Can lead to anxiety, depression, insomnia and 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 seems to influence altered immune response in elders.
• Non-restorative sleep increases stress and weakens immune system.


Ashwagandha Root (and Leaf)
(Withania somnifera)

• Significant stress protecting, anxiolytic, analgesic & anti-inflammatory effects.
• Most calming of adaptogenic herbs.
• Clinical study: 64 subjects with chronic stress randomized 300 mg 2 x day of ashwagandha extract or placebo for 60 days.
• Significant reduction in all stress assessment scales (p<0.0001) and cortisol levels (p=0.0006), relative to placebo.


Ashwagandha and Sleep

• 8-week double-blind, randomized, placebo-controlled study: 125 mg/d or 300 mg ashwagandha extract taken twice daily led to statistically significant improvement in sleep quality, relative to baseline and compared to placebo.
• 10-week study of 60 patients with insomnia and anxiety: 300 mg ashwagandha extract administered twice daily with water or milk significantly improved sleep quality, sleep onset latency, and anxiety, compared to placebo.
• 12-week study of 50 elder patients (65-80 years): significant increase in sleep quality and mental alertness in morning in those taking 600 mg ashwagandha extract, compared to placebo.

Self Soothing

- A good way to deal with anxiety and high stress is to occasionally sidestep the analytical part of your brain by practicing relaxation, meditation and/or using guided imagery.

Mindfulness Meditation

- Helps with stress perception and pain intensity, elevates mood. Quiets stream of thoughts.
- Long-time meditators have greater activation of areas responsible for sustaining attention, processing empathy, integrating emotion and cognition.
- Review of 47 trials found that meditation improves:
  - Anxiety
  - Depression
  - Pain

Resources for Stress Reduction

- Calm – great app for guided meditation, bedtime stories, breathing exercises (free to $60 annual subscription)
- Insight Timer - ~4,000 guided meditations >1,000 teachers (self-compassion, nature, stress, podcasts). Music tracks (free to $5/mo)
- Headspace – meditation, videos, meditations music (free basic course, $12.99 mo, $95/year)
- 10% Happier – performance enhancement. Busy people, stressed lives. (Free one week intro, then $100 per year).
- Buddhify - for the more advanced meditator. Can sort by location, activity and/or emotion. (small monthly fee, premium is $30/yr).

1. Move more. Whether it’s 7-minute workout, cycling, yoga, or long walks - one of surest ways to maintain heart, brain, bone, muscle and immune health is daily exercise. Just do it.
2. Eat food. Minimally processed, low glycemic load, diverse, and largely plant based diet. Organic, local, and/or humanely raised when possible. Avoid endocrine disruptors.
3. Meditate. Meditation widens the gap between trigger and response, allowing you to feel a greater calm and awareness. It’s a game changer for almost anyone.
4. Stay connected. Social isolation and loneliness is as dangerous as being an alcoholic or being obese. Invest in your friends and family.
5. Take a multi. Many lack when it comes to key micronutrients. It can be insurance against the gaps. Age and gender appropriate. Consider additional vitamin D.
6. Be tech smart. Technology makes life easier and more complex. Use blue light blocking glasses at night, make one day each week tech free, and limit email in the evening.
7. Nurture spirit. The search for meaning and purpose is a fundamental part of being human. A richly nourished inner life is a source of strength during hard times. Look inward. Honor mystery.