Anti-biotic Resistance, Natural Immune System Builders

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Lynn Lafferty, PharmD, ND, CNC, CNHP, is a doctor of pharmacy and licensed pharmacist, naturopath, herbalist, nutritionist, and chef who is committed to finding the safest and most effective means to promote health and wellness over disease and illness. She is an assistant professor in family medicine and developing an integrative medicine department at Nova Southeastern University College of Osteopathic Medicine. Dr. Lafferty also has an herbal medicine practice in the Nova Southeastern University Clinic Pharmacy.

Her goal is to help and educate as many people as possible about the amazing possibilities of combining the best of both worlds from modern medicine and age-old traditional approaches.
What is Antibiotic Resistance?

- **Antimicrobial resistance (AMR)**
  - Resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it
- **Resistant microorganisms**
  - Bacteria
  - Fungi
  - Viruses
  - Parasites
- **Evolution of resistant strains is a natural phenomenon that occurs**
  - When microorganisms replicate themselves erroneously
  - When resistant traits are exchanged between them
- **Use and misuse of antimicrobial drugs accelerates the emergence of drug-resistant strains**

Antibiotic Resistance

- **Antimicrobial resistance is one of our most serious health threats**
- **CDC estimates that in the United States:**
  - At least two million people are sickened every year with antibiotic-resistant infections
  - At least 23,000 die as a result
  - Almost 250,000 people each year require hospital care for Clostridium difficile (C. diff) infections (related to antibiotic use and resistance)
  - At least 14,000 people die each year in the United States from C. difficile infections
- **Many of these infections could have been prevented**

Life On This Planet Is Very Intelligent and VERY Adaptable

- **Bacteria have adapted for 3 billion years**
- **Bacteria can produce a new generation every 20 minutes**
- **Bacteria learn how to live and prosper in antimicrobial environments**
- **Sharing resistance: bacteria pass information along to others**
  - They are also communicating across species which was never seen before antibiotics
  - They share resistance information through:
    - Encoding plasmids
    - Using transposons and integrons
    - Using viruses

Altered Uptake

- Most antibiotics (ABs) need to enter the cell to kill them
  - They permeate the cell membrane
  - Some do this by attaching to cellular influxes of materials to live
    - Attach to nutrients
    - Bacteria can alter their permeability

Target Modification

- Bacteria alter their internal structure so the AB cannot affect it the way it needs to
- The AB cannot do anything now to the bacteria because the target structure is altered

Antibiotic Modification

- The bacteria can degrade or destroy the AB
  - Inactivates or disables compounds
  - Ex. enzymes like beta-lactamases and aminoglycoside-modifying enzymes
    - ESBL: Extended-spectrum beta-lactamases
  - NEW: NDM-1 (New Delhi Metallo-beta-lactamase-1) active against carbapenem AB’s
    - Class of beta-lactams that were resistant to ESBL
    - This is carried on plasmids and easily transfer to a wide range of antibiotics

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4311323/
Efflux Pumps

• These are pumps bacteria develop to pump out what they do not want inside the cell
• 5 types that can pump out any chemical
  o Major facilitator super family (MFS)
  o ATP-binding cassette super family (ABC)
  o Small multi-drug resistant family (SMR)
  o Resistance-nodulation-cell division superfamily (RND)
  o Multi-antimicrobial extrusion protein Family (MATE)
• Most Gm+ use MFS
• Most Gm- use RND
**These can also act on bile salts and stomach acid which have their own antimicrobial activity.

Super Adaptability

• Bacteria learn how to live and prosper in antimicrobial environments
• Sharing resistance: bacteria pass information along to others
  o They are also communicating across species which was never seen before antibiotics
  o They share resistance information through
    • Encoding plasmids
    • Using transposons and integrons
    • Using viruses

Plasmids, Transposons and Integrons

• Plasmid is a chromosome independent DNA strand
  o It contains resistance information
  o They pass it to other bacteria
  o They are highly mobile
• Integrons: DNA sequence which integrates into certain sites of the genome structure
  o They transmit resistance and virulence information
• Transposon: unique moveable segment of DNA
  o They move between chromosomes and plasmids
  o They are easily incorporated into DNA
    • Then the physical form of the bacteria is altered
    • They use this to transmit resistance information into environment which is then taken up by other bacteria

Viruses or Bacteriophages

- Transfer resistance information
- Weave into DNA
- Retain resistance information forever
- Bacteria learn at a fast rate

Low Dose Antibiotics are Everywhere

- Water of all industrialized countries
- Chickens and cows
- Acne treatment
- It has now been found that aerobic, anaerobic, Gm+, Gm-, spirochetes, plasmodial parasites all exchange resistance information something that never occurred before ABs

Your antibacterial soap is so dangerous, Minnesota just banned it.
Triclosan
5-chloro-2-(4-dichlorophenyl)phenol

• FDA has asked soap makers to prove it has more effect than washing hands with regular soap
• Endocrine disruptor (EDC)
  - TCS and BP-1 increased LNCaP cell proliferative activity and migration as did dihydrotestosterone (DHT)
• Antibiotic resistance
  

Herbal Therapeutics/ Clinical Nutrition

• Herbal therapeutics/clinical nutrition is an approach informed by science to create balance and wellness based on what the body needs to thrive
• Based on:
  - Physiology
  - Biochemistry
  - Genomics
• Part of integrative medicine
Plants are Multi-faceted

- Drugs: pure chemical derived from plants
- Whole foods and herbs: chemical in a complex chemical matrix
  - Chemical complexity advantage
  - More difficult to research because too many complexities
  - In some cases, the SUM may be greater than an INDIVIDUAL PART
    - Bioavailability, metabolites
    - Better medicinal action with the parts together than separate in some plants

Pharmacology of Herbs

- Phytochemistry: the chemical nature and classification of archetypal plant constituents
- Plants have primary and secondary metabolites
  - Primary metabolites are what sustains the life of the plant:
    - Chlorophyll
    - Proteins
    - Carbohydrates
    - Lipids
  - Secondary metabolites are probably to protect the life of the plant
    - This is where they find new pharmaceuticals

The Plants Immune System: Secondary Components

- Chemical mechanisms for protection
- Alkaloids against pathogens and herbivores
- Glucosinolates protect against insects
- Tannins protect trees from insects and microbial disintegration
- Phytoalexins toxic against fungus
- Flavonoids are inducers of good bacteria
Studies Show Whole Plant Better

- Keung, w. et.al. Potentiation of the bioavailability of Dazin by an extract of Radix puerariae, Proceedings from the National Academy of Science, 1996:93:4284-4288

Synergistic Components

- Lemongrass
  - Geranial and neral individually show antimicrobial activity and myrcene did not
    - BUT when the three are together the myrcene enhanced the other two
  - Same with senna A and senna c from senna—both have laxative effect
    - BUT when they are in 7:3 ratio like they occur naturally they have enhanced effect

Food Chemistry

- Probiotics
  - Good bacteria
- Prebiotics
  - Feeds good bacteria
- Nutrigenomics
  - Food interactions with genes
- Fiber and complexes in food like an apple used as a delivery system
  - Sustain blood sugar
  - Clear toxins

The Role of Gut and Microflora (Probiotics) in Immune System

- The gut has the largest mass of lymphoid tissue in the body
- 60% of the total immunoglobulin produced daily
- Precursors to serotonin and dopamine
- Short Chain Fatty Acids
  - Hormones
  - Cell membrane
  - Immune

Gut Flora

- Millions of bacteria inhabit in large intestine
  - Favorable environment such suitable pH
  - Nutrients for the growth of bacteria
- Most abundant species are anaerobic bacteria
  - There are over 500 different species
  - Beneficial bacterial species or probiotics:
    - Bifidobacteria
    - Lactobacilli
  - Beneficial yeast species or probiotics:
    - Sacchromyces species

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Gut Flora

- Potentially harmful bacteria species:
  - Bacteroides, Peptococci, Staphylococci, Streptococci, Bacilli, Clostridia, Enterobacteria, Fusobacteria, Eubacteria, catenobacteria, and many others
  - Infection

- Yeast
  - Candida Albicans – kept under control by probiotic bacteria
  - Metabolize starch and sugar in absence of bacteria – gives rise to gas and toxic products – causing gut inflammation and alters immune function

Gut Function and Neurotransmitters

- Multiple intracellular and extracellular regulatory factors affect transcription of the tyrosine hydroxylation (TH) gene encoding the rate-limiting enzyme in the biosynthesis of the neurotransmitters dopamine, norepinephrine and epinephrine
- Intestinal tissues are nutritionally significant sites of de novo synthesis of alanine, arginine, glycine, and especially tyrosine

Lymphoid Organs and Tissues

- Lymph nodes
- Thymus
- Spleen
- Gut-associated lymphoid tissue (GALT)
- Tonsils
- Loose connective tissue framework that houses aggregations of lymphocytes
Approximately 80% of Immune System is Located in the Gut

- Gut-associated lymphoid tissue or GALT
- The number of lymphocytes in the GALT is roughly equivalent to those in the spleen
  - Intraepithelial lymphocytes
  - Located “inside” the epithelium
  - Lamina propria lymphocytes
  - Scattered in the lamina propria of the mucosa
  - Majority of these cells are IgA-secreting B cells
  - Peyer’s Patches
  - Lymphoid follicles similar in many ways to lymph nodes, located in the mucosa
  - B lymphocytes predominate in Peyer’s patches
  - Smaller lymphoid nodules can be found throughout the intestinal tract

Important Function of Gut flora

- Aids the gut with the process of digestion
- Plays a part in the absorption of minerals and nutrients
- Synthesizes vitamins
- Helps to break down carcinogens that are found in the diet
- Creates a natural barrier that acts against harmful bacteria, antigens, and toxins
- Helps to protect the body against infection

Many Studies Implicate Bacteria in RA

Change to Active Ingredient Sensitivities

- 5-hydroxy-1,4-naphthoquinone (black walnut)
- Alliin (garlic)
- Arbutin (Arctostaphylos uva ursi)
- Artemisinin (Artemisia sp.)
- Berberine (Goldenseal, uva ursi, berberine sulf.)
- Caprylic acid (fatty acid, octanoic from coconut)
- Carvacrol (oregano)
- Oleuropein (olive leaf)
- Quinic Acid (cat's claw)
- Thymol (thyme, myrrh)
- Undecylenic acid (castor oil)

Natural Antimicrobials/Antifungals

ANTIBACTERIAL
- Berberine herbs
- Citrus seed extract
- Oregon grape root
- Garlic
- Red thyme oil
- Oregano oil
- Caprylic acid
- Uva ursi

ANTIFUNGALS
- Berberine herbs
- Citrus seed extract
- Black walnut hull
- Garlic
- Red thyme oil
- Oregano oil
- Caprylic acid
- Uva ursi

Autoimmune Diseases and Gut Flora

- Celiac disease
  - Gluten intolerance
  - More than 3 million Americans, according to the University of Chicago's Celiac Disease Center
  - Gluten prompts your “autoimmune” response to attack your villi, the small finger-like nodules in your small intestine
    - Symptoms, including abdominal discomfort and bloating, gas, constipation or diarrhea
    - Malnutrition, neurological symptoms and increased risk of cancer in your intestines

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Autoimmune Diseases and Gut Flora

- Antibodies to Yersinia enterocolitica in thyroid disease.
  - The prevalence of elevated antibody titers against Yersinia enterocolitica was studied in normal subjects, patients with a variety of nonthyroidal illnesses, and patients with thyroid disease. In contrast to the low prevalence of antibodies in controls (less than 8%), 48 of 67 patients (75%) with a variety of thyroid disorders had titers greater than 1:8. Antibodies were found in 24 of 36 patients with Graves’ disease, five of six with autonomous adenoma, seven of seven with Hashimoto’s thyroiditis, three of five with idiopathic primary hypothyroidism, four of 11 with nontoxic nodular goiter, and one of two with thyroid carcinoma. Antibodies to serotype 3 were the most prevalent, occurred in the highest titers, and were found particularly in patients with Graves’ disease. These observations indicate that in spite of the infrequent occurrence of yersinia infection in the United States as compared with Scandinavia, patients with thyroid disorders have a higher prevalence of antibodies to Yersinia than normal subjects or patients with other disorders.

Autoimmune Diseases and Gut Flora

- When Good Germs Go Bad: “Friendly” Gut Bacteria Can Trigger Rheumatoid Arthritis in Mice
  - Also talks about Type I diabetes being caused this way as well
  - Only 50% of identical twins get type I diabetes

Autoimmune Diseases and Gut Flora

- Host–microflora interaction in Systemic Lupus Erythematosus (SLE): colonization resistance of the indigenous bacteria of the intestinal tract
  - Long polar fimbriae have been identified as a key factor that enable adherent-invasive Escherichia coli to target Peyer’s patches in the ileum of patients with Crohn’s disease, report a multinational research team

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Autoimmune Diseases and Gut Flora

Probiotic Bacteria Could Help Treat Crohn’s Disease
ScienceDaily (Mar. 31, 2011) — New research suggests that infection with a probiotic strain of E. coli bacteria could help treat and reduce the negative effects of another E. coli infection that may be associated with Crohn’s disease. Researchers from the University of Auckland, New Zealand publish their results in the April 2011 issue of the journal Applied and Environmental Microbiology.

Role of Bacteria

Friendly Bacteria
L. acidophilus, L. salivarius, L. casei, L. thermophilus, B. bifidum, B. longum, etc.

Unfriendly Bacteria
Pathogenic bacteria and fungi, such as Candida albicans, etc.

Mechanism of Benefits

- Co-localisation resistance
- Maintain barrier function
- Modulation of signal transduction
- Enhance microbial flora
- Metabolic effects
- Adaptive immunomodulation
- Innate immune responses
- Maintain homeostasis and health
Prebiotics

- Non-digestible carbohydrates that selectively stimulate the growth and activity of beneficial bacteria in the intestines
  - Lactobacilli and bifidobacteria
- As a result of its chemical structure, prebiotics are not absorbed in the small intestines
  - Undergo bacterial fermentation in colon to produce energy, metabolic substrates, and nutrients

Leukocytes Mostly Made in Bone

- Basophils
- Eosinophils
- Lymphocytes (T cells and B cells)
  - Lymph tissues: spleen, thymus, gut
- Monocytes
- Neutrophils

Bone: Specialized Connective Tissue

- Skeletal mass 30% Osteoid matrix
  - Collagen
  - Hyaluronic acid
  - Chondroitin sulfate
  - Vit. K-dependent protein called osteocalcin
    - Important calcium binding molecule
  - Matrix of calcium phosphate (hydroxyapatite) and bone cells
Bone Factors

- Made mostly of collagen, calcium phosphate
- Trace minerals: Ca, Cu, Mn and Zn; Si, B, Vit.K, Cr, Strontium
- Growth hormone
- Parathyroid hormone promotes osteoblasts
- Estrogens slows up the destruction of bone
- Calcitonin and thyroid stimulating hormone (TSH) inhibit osteoclasts
- Osteoprotegerin is a protein secreted by osteoblasts and their precursors (thus a cytokine) that also inhibits the production and activity of osteoclasts
- Lepin regulates the balance between osteoblast and osteoclast activity
- Serotonin may suppress osteoblasts

Vitamin C

- Vitamin C, an essential cellular nutrient, is involved in a variety of metabolic reactions and is an important antioxidant in biological systems
- Catecholamines and corticosterone require vitamin C for their synthesis in the adrenals and to protect them from oxidation\(^1\) \(^2\)
- Very important in collagen formation

Thymus

- Hematopoietic precursors from bone in the bone marrow, referred to as thymocytes, mature into T-cells
- Mature T-cells emigrate from the thymus and constitute the peripheral T-cell
  - Responsible for directing many facets of the adaptive immune system
  - Loss in early life = severe immune deficiencies
  - Older turns fat but still endocrine function


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Chapter 43 – Thymus and Parathyroid Organogenesis

- "The thymus is the principal site of T cell development and therefore is of central importance within the immune system: congenital athymia results in profound immunodeficiency, while perturbed thymic function can lead to autoimmunity... T cell development diminishes significantly with age. This has implications for immune function in the aging population, and in clinical procedures such as bone marrow and solid organ transplantation, where thymic function is required for T cell reconstitution and/or tolerance induction. Interest therefore exists in enhancing immune reconstitution through regenerative or cell therapies for boosting thymus activity in vivo, or providing customized in vitro generated T cell repertoires for adoptive transfer."

Kathy O'Neill, Craig Scofield Nowell, Ellen Richie, Nancy Ruth Manley, Catherine Clare Blackburn
Principles of Tissue Engineering (Fourth Edition) 2014, Pages 869–897

Lymphocytes

- Large and small
- Natural killer (NK) cells
  - Makes cytokines called interferons
  - Kills viruses and tumors
    - By surface protein MHC (major histocompatibility complex)
- T cells (from thymus)
  - Cell mediated
- B cells (from bones)
  - Humoral

Spleen

- Old red blood cells filtered and holds a reserve of blood in case of hemorrhagic shock
- Part of the lymphatic system (structure of a large lymph node)
- Synthesizes antibodies in its white pulp and removes antibody-coated bacteria
  - Size: 11cm, Wt: 5.3 oz-7.1 oz.
  - Like thymus, possess only efferent lymphatic vessels (gastric arteries and splenic arteries supply blood)
Immune Builders and Natural Antibiotics

Natural Ways to Boost Immune

- Nutrition
- Sleep
- Laughter
- Manipulation
- Non-stressful stress
- Vitamins
- Minerals
- Herbs
- Whole foods (i.e. animal tissue factors)

S1gA Release
What Do You Think Most People Eat?

Beneficial Aspects of Probiotics

- Enhancement of the epithelial barrier
- Adhesion to intestinal mucosa
- Lactose digestion
- pH-lowering capacity
- Concomitant inhibition of pathogen adhesion and modulation of the immune system by inducing the recruitment of immune cells and activating appropriate immune and inflammatory responses


1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), the Active Form of Vitamin D

- Key-player in bone formation
  - Regulate calcium and phosphorus metabolism
  - Calcium absorption
- Immunomodulator
  - Monocytes, macrophages, dendritic cells (DCs), as well as T-lymphocytes and B-lymphocytes
  - Immune cells express vitamin D-activating enzymes, allowing local conversion of inactive vitamin D into 1,25(OH)₂D₃ within the immune system
Zinc

- Homeostasis of immune system
  - Deficiency can lead to pro-inflammatory cytokines
  - Very important in T cell differentiation
- The level of dietary Zn examined is a critical component of any investigation of the effect of Zn status on intestinal immune function and systemic immune function
  - Changed bacteria and gut permeability

Iron

- Iron homeostasis and macrophage biology are closely interconnected
  - On the one hand, iron exerts multiple effects on macrophage polarization and functionality
  - On the other hand, macrophages are central for mammalian iron homeostasis
  - The phagocytosis of senescent erythrocytes and their degradation by macrophages enable efficient recycling of iron and the maintenance of systemic iron balance
- Iron deficiency and infections are closely related in children

Selenium (Important with Vitamin E)

- Upregulates the expression of the T-cell high-affinity IL-2 receptor and provides a vehicle for enhanced T-cell responses
  - Stimulatory effect on antibody production
  - Age-related decreases in cellular immunity can be partially reversed by Se supplementation increasing responsiveness to IL-2
  - Prevents oxidative-stress-induced damage to immune cells
  - Alters platelet aggregation by decreasing the ratio of thromboxane to leukotriene production
Garlic

Antimicrobial sensitivity tests were carried out on Escherichia coli, Shigella sp, Salmonella sp, and Proteus mirabilis using standard procedures. Significant differences (p < 0.01) were seen in the effect of the antimicrobial agents (garlic, ciprofloxacin and ampicillin), and in the sensitivities of the microbial species (p < 0.05) to the antimicrobial agents were observed. The gram-negative diarrheagenic pathogens from the stool samples were highly sensitive to garlic, while ciprofloxacin (CPX) was most effective against E. coli.

No isolates were resistant to garlic, making it a promising antimicrobial agent. It appears that antibiotics that interfere with DNA and RNA syntheses, such as garlic does, could constitute an effective partner in the synergic effect of garlic currently being investigated worldwide.

Garlic

- Raw juice of garlic was found to be effective against many common pathogenic bacteria-intestinal bacteria
- Garlic is effective even against those strains that have become resistant to antibiotics
- The combination of garlic with antibiotics leads to partial or total synergism
- Complete lack of resistance has been observed repeatedly
- Even toxin production by microorganisms is prevented by garlic
- Even some antibiotic-resistant H. pylori strains are susceptible to garlic

Goldenseal

- *Hydrastis canadensis* (goldenseal) is one of a number of plants that contain the alkaloid berberine
- Berberine extracts and decoctions have demonstrated significant antimicrobial activity against a variety of organisms
  - Used clinically to treat bacterial diarrhea, intestinal parasite infections, and ocular trachoma infection
Berberine: New perspectives for old remedies

Berberine exerts antimicrobial effects being a NorA substrate able of accumulating in bacterial cells and of binding both single- and double-stranded DNA, thus leading to bacterial death by DNA damage. It has a weak activity against Gram-negative bacteria, and is more potent against Gram-positive bacteria, including Mycobacterium tuberculosis and MRSA (Methicillin-Resistant Staphylococcus aureus), by the MDR pump NorA inhibition. It also exhibits antifungal activity on Aspergillus, Penicillium, Candida, and Cryptococcus.

Oregano Oil

- Contains the constituents carvacrol and thymol which have anthelmintic, fungicidal, and irritant properties.
- Oregano oil also has in vitro activity against a variety of common gram positive and gram negative organisms, including: Acinetobacter calcoaceticus, Enterococcus fecalis, Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella species, Serratia marcescens, Staphylococcus aureus, and the yeast Candida albicans.
- The carvacrol and thymol constituents also inhibit bacterial growth, with additive or possibly synergistic activity in oregano oil.
  - Carvacrol has a bactericidal effect on Bacillus cereus, a common food pathogen, by altering bacterial membrane permeability.
- Oregano oil and carvacrol in vitro has anti-influenza virus activity.
- Oregano oil seems to inhibit the growth intestinal parasites in vivo.

Thank You