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IMMUNOLOGY

Contributors

5 Immunology in Rheumatology: It Starts from Outside Our Body to Within
By John A. Goldman, MD

6 The History of Our Immune Response From B Cells to T Cells and Everything in Between
By Gary E. Myerson, MD

10 Microbiome – You are Never Alone: Microbial Ecosystems in Our Bodies Influence Everything from Immunity to Behavior.
By John A. Goldman, MD

18 IgG4-Related Disease: An Emerging Condition
By Arezou Khosroshahi, MD

24 Giant Cell Arteritis: A Brief Review
By Athan Tiliakos, D.O.

27 Rheumatoid Arthritis: New Therapies and a Better Understanding of What Triggers the Disease Provide Hope for the Future
By W. Hayes Wilson, MD

28 Lupus: The Specter of the Wolf
By Glenn R. Parris, MD

33 Biologics and Biosimilars
By Bridget M. Wright, MD

36 SPOTLIGHT
The Affordable Care Act
By Helen Kelley

40 MEDICAL ASSOCIATION OF ATLANTA
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Arezou Khosroshahi, MD
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The immune system is there to protect you, but it can go awry. As rheumatologists, we carefully study diseases caused by disorders of the immune system. There are diseases caused by immunodeficiency when the immune system fails to maintain itself, such as immunoglobulin deficiency, or when it fails due to an infection such as HIV, where there is an acquired immunodeficiency of CD4+ helper T cells, dendritic cells and macrophages leading to AIDS.

There are those settings where the immune system is hyperactive and the response can be detrimental to the host, such as asthma. Finally there is that of an aberrant immune response, when the immune system that is supposed to protect the body turns against us. This is autoimmunity.

Rheumatologists are thoughtful physicians who are trained to do in-depth evaluations of our patients. We know the immune system is involved in various daily medical settings that may be more subtle: respiratory infections, gastroenteritis or an upper respiratory infection, when the immune system is involved but not heralded as a major player. It may be less apparent in cardiovascular disease and more apparent in pulmonary disease, neurological disease, dermatology, endocrinology, metabolic bone disease, nephrology and oncology.

This issue of Atlanta Medicine presents only a small portion of the types of problems we as rheumatologists confront on a daily basis. We emphasize here a variety of the issues. We need to understand how the immune system performs to help understand the pathogenesis of those we are assessing. We think of a patient’s genetic risk factors, how these are affected by epigenetic phenomena, and how these influence the body’s responses. The microbiome is extensive and as we are learning more, we see how it influences our body’s response, both for the good of how it protects us and the bad of how it does not.

A recently discovered immunological disease process, IgG4-related disease, helps explain one of the clinical dilemmas we had been confronted with. Now we have a name and somewhat of an explanation. We see clinical syndromes every day we cannot define, and in the future there will be other discoveries.

Blood vessels go all over our body and can become inflamed. This inflammation can occur in many ways, some of which may include immune attacks. Giant cell arteritis is an example of this.

Regarding how we treat diseases, new, exciting therapeutic tools in the biologics and certain small molecules have been developed. These have been used in rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) to name a few.
Centuries ago, geography itself served as the primary barrier to disease exposure. But man’s exploration of the planet, enhanced by progressive technological expertise, has permitted both exposure to and expansion of diseases worldwide. With our increasing knowledge of science, however, a better understanding of the specific components of the immune response has led to numerous diseases either being reduced or eliminated.

The immune response is an ancient system. Certain components, however, have not significantly changed over the millions of years of existence of species with vertebrae. The Homo sapiens – modern man – and Homo erectus, which lived from 1.9 million years ago to 143,000 years ago, indeed possessed an immune system similar to ours. The innate immune response has been present throughout this entire period. It has been our “equalizer” in dealing with the microscopic environment that envelops us. We have made “friends” with many microbes, resulting in relationships that are symbiotic, while others are indeed antagonistic or parasitic.

It is this inherent, genetically provided, innate response that is our first line of defense – our barriers against invaders both physically and chemically. Physicians have a tendency to under appreciate the innate immune response, since we have little ability to change or alter it. The adaptive or acquired immune response, along with our body’s ability to develop antibodies, has allowed us to improve or enhance our own existence. The development and advancement of biologic therapies such as monoclonal antibodies has furthered our ability to amend that immune response.

I remember my first immunology textbook back when I was a senior in medical school in 1976-1977. This was a small paperback, Essentials of Immunology, by Benjamin Lee Gordan, MD. It was 267 pages in large print. At that time, it was believed that T cells were from the thymus gland and B cells from the “bursa of fabricius of the bird.” Our terminology and understanding of the immune response has significantly evolved from that time.

Physically, our first line of defense includes the skin and lining surfaces of the internal body organs. Chemically, enzymes in body secretions, including lysozymes, phospholipases and defensins, disrupt cell membranes promoting cell death. Periodically, the anatomical barriers are penetrated, and an “acute inflammatory reaction” follows.

The release of acute phase reactants (transferrin, CRP, interferons and interleukins) result in clinical symptoms of fever, rubor, color, dolor or hot, red and swollen areas. The protective phagocytic cells of the our body, which include the neutrophils, macrophages, dendritic cells, natural killer or NK cells and eosinophils are the major players in identifying and responding to these microscopic invaders.

The phagocytic cells patrol the body searching for pathogens. Frequently, they are directed to specific locations via protein communicators of inflammation (cytokines),
where they identify, engulf and destroy the pathogens. These cells are primary players of the innate immune response – probably the oldest form of the host defense system.

The innate immune response is triggered when microbes (bacteria, virus and fungi) are “identified.” Commonly shared molecules referred to as PAMPS (pathogen-associated molecular patterns) are on or attached to the cell membranes of these pathogens. These include lipopolysaccharides (LPS), lipoteichoic acid, flagellin and RNA viruses, amongst others. These molecules are recognized by receptors on the phagocytic cells (monocytes, macrophages and dendritic cells) called pattern recognition receptors (PRRs). A large group of PRRs are a specific subgroup entitled Toll-like receptors (TLRs). These highly specific receptors, numbered 1 through 13, identify and bind PAMPS, resulting in cytokine production and triggering inflammation.

The complement cascade is also a major component of the innate immune response. This system, the body’s “sanitation department,” further serves as an identifier and clearing house of pathogens by promoting vascular permeability, recruitment of phagocytic cells and ultimately the opsonization of bacteria and immune complexes.

Opsonization refers to the coating and subsequent marking of bacteria for future destruction. A large component of opsonization occurs in the spleen, which is why splenectomized patients need vaccinations against bacteria. The complement system, as a component of the innate immune response, also serves as a major cross-reactor with the adaptive or acquired immune response.

With complement activation, more rapid antibody binding occurs, promoting or “complementing” pathogen clearance. Clinically, we measure the activity of the complement system in its entirety by measuring a CH 50 blood level. Individual measurement of levels C3 and C4, especially in patients with autoimmune diseases, in which the self is recognized as foreign, results in overactivity of the complement cascade and the inability to catch up with the excessive immune complex formation. Subsequently, low levels of C3 and C4 occur.

When the system specimen normalizes, levels return to within the normal range. Subsequently, low levels of CH 50 and C3 and C4 may reflect pathogenic status, but higher levels indeed do not.

In other words, the innate immune response is a nonspecific, immediate and non-antigen specific reaction. Additionally, immunological memory does not develop. However, survival necessitates long-term protection, and this is where our adaptive or acquired immune response comes into play.

Immunological memory is the development of antibodies – our Army, Navy, Air Force and Marines. After an initial exposure and response to a specific pathogen, subsequent encounters with the same organism result in an enhanced response. The system, however, has a “lag time” of approximately 10 to 14 days for antigen-specific antibodies to develop.

All cells of the immune system have their origin in the bone marrow. The myeloid series primarily produces the cells of the innate immune system, including the neutrophils, monocytes and dendritic cells. On the other hand, the lymphoid series (lymphocytes) produces cells for the acquired or adaptive immune response.

The T cells, which are produced in the bone marrow, undergo differentiation into their distinct types under the influence of the thymus gland. B cells, which are “born” in the bone marrow, become mature in the lymph nodes and the spleen. There is tremendous amount of crossover in the function and activity of both systems, utilizing the myeloid series as an active component for stimulation and activation of the acquired immune response.
T cell Stimulation and Activation

T cells are involved in the cell-mediated immune response. They have no cytotoxic activity and do not kill infected cells or clear pathogens directly. Instead, they control the immune response by directing other cells to perform these tasks. The cytokines the T cells produce are the "protein communicators of inflammation."

Most physicians will recognize three of these – TNF alpha and the interleukins IL-1 and IL-6. These are the primary players in autoimmune diseases, including rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis and inflammatory bowel disease, specifically Crohn’s. They are also actively involved in uveitis and sarcoidosis.

The T cell begins as a “naïve” cell, having been produced but not yet directed in its function. It requires antigen presentation in order for it to become activated. These antigen-presenting cells (APC) include the macrophage, dendritic cell and the B cell. The identifying amino acid sequence of the antigen, referred to as the antigen fragment, is inserted into the major histo-compatibility complex (MHC). The APC presents the antigen to the naïve T cell via its receptor, MHC. The recognized antigen will bind to the T cell receptor (TCR), on the T cell. Depending on the APC cell type and the predominance of surrounding cytokines, T cells will mature or differentiate in one of four directions.

1. TH 1 cells. APCs include the macrophages and dendritic cells. IL 12 and INF (interferon) gamma are the cytokines that drive differentiation. This type of T cell usually develops from exposure to intracellular bacteria, fungus or viruses.

2. TH 17 cells. Neutrophils; IL 23, IL-1, IL-6. Usually from exposure of extracellular bacteria and fungi.

3. TH 2 cells. Eosinophils and basophils. IL-4. Usually from exposure to parasites.


There is, however, cross stimulation and inhibition depending on which interleukin predominates. IL-6 inhibits TGF beta, therefore driving TH 17 production and reducing Treg production. IL 6+ TGF beta drives the production TH 17 cells. IL-4, while driving TH2 production, inhibits TH 17 production.

On the cell membrane of many T cells are glycoproteins CD4 and CD8. (CD is abbreviation for cluster differentiation.) Cells with the CD4 glycoprotein are frequently referred to as helper cells, and those with CD8 glycoprotein are referred to as cytotoxic T cells. CD4 helper cells assist in the maturation of B cells into plasma cells and memory B cells. They also assist in the activation of cytotoxic T cells and macrophages.

Cytotoxic CD8 cells destroy viral-infected and tumor cells and also play a role in transplant rejection.

Types of B cells

The B lymphocytes (B cells) play a large role in the humoral immune response, ultimately producing plasma cells that produce antibodies. The B cell develops through several stages. In the bone marrow, it begins as a progenitor cell, then progresses to a pro-B cell and finally a pre-B cell.

At this point, it leaves the bone marrow to mature in the lymph nodes and spleen, where it becomes “exposed” to the pathogenic environment. As it matures, it develops three surface receptors – Blys, TACI and the B-cell receptor (BCR).

When these receptors are bound, the cell matures and continues to exist. Failure to bind these receptors results in apoptosis or programmed cell death. This has become a recent important discovery, since the drug for the treatment of lupus works by inhibiting Blys cell surface, the cell surface receptors.

B cells exist as clones. All B cells derived from a specific clone can produce “progenies,” which can recognize specific antigens and produce specific antibodies for generations. With each cycle of exposure, the number of surviving memory cells continues to increase. This is the basis of “immunogenic” memory.

There are 3 B cell types;

Plasma B cells. The cells produce large amounts of antibodies or immunoglobulins, including IgG, IgA, IgM and IgE. These immunoglobulins are hallmarks of our defense system. We’re aware that deficiencies in any one of them or their subtypes results in the development of recurrent infections. Specific types of intravenous and subcutaneous
gammaglobulin are available for those deficiency states.

Memory B cells. These cells are formed from activated B cells that are specific to the antigen encountered during the primary immune response. These cells are capable of living a long time and can respond quickly following a second exposure to the same antigen.

B1 cells and B-2 cells. B1 cells express high levels of IgM greater than IgG and are polyspecific, meaning that they have the ability to produce a low-level response to many antigens.

Unlike the T cell, the B cell does not need the antigen presented to it. It recognizes the antigen in the blood or lymphatic system and engulfs it. It can then act as an antigen-presenting cell itself by displaying its antigen rebound to its unique MHC on the cell surface, allowing a T cell to bind to it.

Through a costimulatory mechanism necessitating a second binding site to be activated, cytokines can then be released. The cytokines released by that T cell further propagate the B cell into its mature state, producing plasma cells and more immunoglobulins. Antibodies bind to their specific antigens, forming immune-complexes. These complexes are then “cleaved” by the complement system and eliminated through the reticular endothelial.

Autoimmune diseases result from aberrant antibody production. These autoantibodies are actually produced on a regular basis by all individuals. Fortunately, over 90 percent of them undergo spontaneous apoptosis and never progress. The development of anti-B cell antibody medications predominantly work by interfering with the B cell during its maturation. The current available medications are being utilized in both oncology and rheumatology.

Remember that the baby’s immune system is mom’s at birth, with its own production developing in approximately three months.

In the H. G Wells classic science fiction novel War of the Worlds, which was first published in the 1890s, the narrator eloquently describes on day 15 “the far advanced Martians invaded the earth, began to destroy mankind and make the planet its own. As their overturned war machines ... laid stark and silent, the Martians were dead – slain by the putrefactive and disease bacteria against which their systems were unprepared. ... After all man’s devices had failed, by the humblest thing that God, in his wisdom and put on this earth ... these germs of disease had taken toll on humanity since the beginning of things – taken toll on her pre-human ancestors since life began here. But by virtue of this natural selection of our kind, we have developed resisting power; to no germs do we succumb without a struggle – our living frames are altogether immune. But there are no bacteria on Mars ... our microscopic allies began to work their overthrow... it was inevitable!! ■
A microbiome is like the pilot fish that congregates around sharks and other species. It eats ectoparasites on and leftovers around the host species. We are covered inside and out with microbiomes and there are a variety of new microbes whose names are unfamiliar and which cannot be cultured.

A microbiome is "the ecological community of commensal (where one organism benefits without affecting the other), symbiotic (meaning that both symbionts depend on each other for survival) and pathogenic microorganisms that literally share our body space." In general they are not pathogenic.

The term “microbiome” was originally coined in 2001 by Joshua Lederberg, who argued the importance of microorganisms inhabiting the human body in health and disease. The word signifies the ecological community of commensal, symbiotic and pathogenic microorganisms that literally share our body space and have been all but ignored as determinants of health and disease.(1, 2)

The Enemy – and Friend – Within

In and on the human body, there are over 10 times more microbial cells than human cells, although the entire microbiome only weighs about 200 grams (7.1 oz.) – others estimate as high as 3 pounds (approximately 48 ounces or 1,400 grams). Since its existence was not generally recognized until the late 1990s, it has been suggested that it is a new organ that has been recently discovered.

There are an estimated 100 trillion microbes, and most of these cannot be cultured. DNA sequencing techniques have found a majority of these microbes.

The human microbiome may be implicated in infectogenomics in diverse illnesses immune-related and non-related, such as cancer, inflammatory bowel disease, rheumatoid arthritis, psoriasis, bacterial vaginosis, obesity, fibromyalgia and periodontitis. Microbes in our body can modify the production of neurotransmitters known to be found in the brain, having an impact on psychiatric disease and neuro-chemical imbalances. Microbiomics have already revealed these vast, immensely powerful ecosystems of bacteria and viruses in every niche scientists have investigated. They have found distinct microbiomes in every orifice and a complex web of microbial interactions and metabolic products influencing every part of our lives. Of note, microbiomes are being characterized in many other environments as well, including soil, seawater and freshwater systems.(3)

Skin

While there is focus on the gut, there is a microbiome in every other body area, including orifices, lungs and the skin. Many of them are bacteria, of which there are around 1,000 species upon human skin from 19 phyla.[1-4] It has been estimated that the total number of bacteria on an average is 1 trillion, outnumbering cells 10 to 1.[3-4] Most were found in the superficial layers of the epidermis and the upper parts of hair follicles.

Microbes present on the skin greatly impact the functions of human immunity. The skin immune system should be considered a collective mixture of elements from the host and microbes acting in a mutualistic relationship.(5) In the microbiome, many different microbes coexist together within a body area like the skin (see Figure 1). These microbes differ among different people.

Rheumatoid Arthritis

In Rheumatoid Arthritis, Scher et al. evaluated the gut and performed 16S sequencing on 114 stool samples from rheumatoid arthritis patients and controls and shotgun sequencing on a subset of 44 such samples.(6) They identified the presence of Prevotella copri as strongly correlated with disease in new-onset untreated rheumatoid arthritis.
(NORA) patients. Increases in Prevotella abundance correlated with a reduction in Bacteroides and a loss of reportedly beneficial microbes in NORA subjects. Gut bacteria produce compounds that appear to modulate inflammation. Years before Joshua Lederberg coined the term microbiome, J. Claude Bennet, MD, from UAB had speculated on the gut and its relationship to rheumatoid arthritis and immune-mediated disease. His clinical research focused on the structures of rheumatoid factors and relationships to various infectious agents as initiators of the rheumatoid process. He had published on the infectious etiology of rheumatoid arthritis, including bacterial antigen load in the human gut. He discussed the presence of peptidoglycan immune complexes in rheumatoid arthritis. He did mass spectrometric evaluation of synovial tissue and found muramic acid, which is not synthesized in the body but is present in the peptidoglycans of bacterial cell wall.

Perhaps it’s a paradox, but we know now these infectious agents in microbiome may also inhibit the rheumatoid activity. The implication that bacteria can prevent disease is prompting some rethinking in the drug industry. "When we start talking about bugs in the realm of pharmaceuticals we always think about killing them, but investigators are taking the opposite tack, developing new databases and computer algorithms to identify ways to restore healthy microbiomes. These microbiomes can be anti-inflammatory and protective," says Dr. Bennet.

**RA and Periodontal Disease**

Studies in rheumatoid arthritis have also focused on periodontal disease (PD). Scher et al. found that the more advanced forms of periodontitis were already present at disease onset in patients with new-onset RA. The subgingival microbiota observed in patients with new-onset RA was distinct from that found in healthy controls. In most cases, however, these microbial differences could be attributed to the severity of PD and were not inherent to RA.

The presence and abundance of Porphyromonas gingivalis (PG) were also directly associated with the severity of PD and were not unique to RA. The presence of PG was not correlated with anti–citrullinated protein antibody (ACPA) titers.

Overall, exposure to PG was similar between patients with new-onset RA and controls, observed in 78 percent
of patients and 83 percent of controls. The presence and abundance of Anaeroglobus geminatus correlated with the presence of ACPAs/rheumatoid factor. Prevotella and Leptotrichia species were the only characteristic taxa observed in patients with new-onset RA irrespective of PD status.\(^{10}\)

There is increased loss of periodontal attachment and alveolar bone in early rheumatoid arthritis, and patients should be informed that they have a higher risk of periodontal disease. It may be beneficial for these patients to get immediate dental care.\(^{11}\)

There are also differences in lung microbiota between arthritis-free Ab (+) cases that are at risk for future RA and control subjects. This raises the possibility of a mechanistic link between the lung microbiome, mucosal inflammation and generation of RA-related autoimmunity.\(^{12}\)

### Human Microbiome Project\(^{13}\)

“The Common Fund’s Human Microbiome Project (HMP) program (FY2007-2015) aims to develop tools and datasets for the research community for studying the role of these microbes in human health and disease. The first phase of HMP (FY2007-2012) characterized the composition and diversity of microbial communities that inhabit major mucosal surfaces of the human body, including nasal passages, oral cavities, skin, gastrointestinal tract and urogenital tract, and evaluated the genetic metabolic potential of these communities. The current phase of HMP (FY2013-2015) is focused on the creation of the first integrated dataset of biological properties from both the microbiome and host from cohort studies of microbiome-associated diseases.”\(^{13}\)

Microscopic study of the healthy human body has demonstrated that microbial cells outnumber human cells by about 10 to one. Until recently though, this abundant community of human-associated microbes remained largely unstudied, leaving their influence upon human development, physiology, immunity and nutrition almost entirely unknown. The National Institutes of Health (NIH) Common Fund Human Microbiome Project (HMP) was established with the mission of generating research resources enabling comprehensive characterization of the human microbiota and analysis of their role in human health and disease.

Traditionally, microorganisms have been studied as cultures in the laboratory. However the vast majority of human-associated microbial species have never been successfully isolated in the laboratory, presumably because their growth is dependent upon specific conditions or substances that have not been duplicated in the laboratory. Advances in DNA sequencing technologies have created a new field of research, called metagenomics, which allows analysis of genetic material harvested directly from microbial communities.

The advent of fast, cheap DNA sequencing technologies has allowed scientists to probe a longstanding question: How many microbial species are there, and exactly what are they doing? Obviously, this tells us we are not alone. Until recently, researchers could only study microorganisms that could be cultured in the lab, leaving an unknown but presumably large number of species unexamined.

In the HMP, this approach is complementing genetic analyses of available reference strains, providing unprecedented information about the complexity of human-associated microbial communities. Other advanced ‘omics technologies like transcriptomics, proteomics and metabolomics, which measures the biological properties of whole microbial communities, are being used to provide insights into how the microbiome and human host interact to support health or to trigger disease.

Initiatives for the first phase of HMP (FY2007-2012) focused on the development of metagenomics datasets and computational tools for characterizing the microbiome in healthy adults and in cohorts of specific microbiome-associated diseases

### Studying the Microbiome

The problem of elucidating the human microbiome is essentially identifying the members of a microbial community that includes bacteria, eukaryotes and viruses. This is done primarily using DNA-based studies, although RNA-, protein- and metabolite-based studies are also performed (see Figure 2).

One of the challenges that is present in human microbiome studies but not in other metagenomic studies is to avoid including the host DNA in the study.\(^{13}\)

On Oct. 4, 2013, scientists working on the frontiers of human microbiomics met at The New York Academy of Sciences (NYAS)\(^{11}\) to discuss the profound effects our personal microbiomes have on health and disease and to ponder the possibilities of a new era of microbially based medicine. The Microbiome in Health, Disease and Therapeutics: Bugs, Guts and Drugs was presented by the Academy’s Biochemical Pharmacology Discussion Group.\(^{11}\)

The microbiome of the human gut contains over 10 million distinct microbial genes, utterly eclipsing the human genome in genetic potential. While less than 1 percent human in terms of actual gene activity, the microbial gene products in turn produce thousands of metabolites, many of which appear to have far-reaching physiological effects on everything from immunity to appetite. The production does not come from one microbe but a whole community.
of microbes. The new tools can map the geography of a patient’s microbiome in a matter of minutes.

**Drug Metabolism**

Similar processes can affect drug metabolism. “If you modulate the microbiome, you change the signaling, which changes ... the way that drugs actually work in the body,” said Jeremy K. Nicholson at a recent NYAS meeting. Such differences could explain many cases of idiosyncratic toxicity, in which a drug that is safe and effective in most patients becomes dangerous or useless in a few.

**Immune Responses in the Gut**

The microbiome is an integral part of human physiology. The composition and metabolic activity of the intestinal microbiome, as a whole community, exerts
a profound influence on mucosal immune regulation. The microbiome produces short-chain fatty acids (SCFA), polysaccharide A (PSA), alpha-galactosylceramide and tryptophan metabolites, which can induce IL-22, Reg3y, IgA and IL-17 responses.

Epithelial cells directly participate in immunological surveillance and direction of host responses in the gut and can express numerous pattern recognition receptors, including Toll Receptors TLR5, TLR1, TLR2, TLR3, TLR9 and NOD2, as well as produce chemotactic factors for both myeloid and lymphoid cells following inflammatory stimulation (14). Within the epithelium and in the underlying lamina propria resides a population of innate lymphoid cells that, following stimulation, can become activated and produce effector cytokines and exert both protective and pathogenic roles during inflammation. Lamina propria dendritic cells (LPDCs) play a large role in determining whether the response to a particular antigen will be inflammatory or anti-inflammatory. (14)

The problem however is that much of what is known about microbiome-host immune interactions has come from the study of single bacterial members of the gastrointestinal microbiome and their impact on intestinal mucosal immunity. There are multiple microbes in the microbiome, not just single bacteria.

**Autoimmunity and the Microbiome, Exposome, Infectome**

The catastrophic failure of human metabolism observed in autoimmune disease results from a common underlying pathogenesis – the successive accumulation of pathogens into the microbiome over time, and the ability of such pathogens to dysregulate gene transcription, translation and human metabolic processes.

Dysregulation of the vitamin D receptor has been proposed. (15) Another theory is that autoimmune diseases are more likely passed in families because of the inheritance of a familial microbiome, rather than Mendelian inheritance of genetic abnormalities. The speculation is that we can stimulate innate immune defenses and allow patients to target pathogens, but cell death results in immunopathology. (16)

Autoimmunity is a case of mistaken identity: The immune system reacts to self-tissues and cells as if they were pathogens. (16) Autoimmune reactions can be both advanced or blocked by the commensal microbiota,
which can affect innate and adaptive arms of immune responses as well as the mechanisms of “innate-adaptive connection.”

Whether specific microbial lineages affect immunity and autoimmunity (the “specific lineage hypothesis”) or multiple lineages can tip the homeostatic balance that regulates host/microbiota homeostasis toward reduced or enhanced host reactivity (the “balanced signal hypothesis”) is still unknown. The complexity of host/microbiota interactions needs to be fully appreciated in order to find the means for prophylaxis and treatment of autoimmune disorders. This is certainly a different way to look at immunity and autoimmune disease.

The “exposome” is a term recently used to describe all environmental factors, both exogenous and endogenous. The concept of the “infectome,” which is part of the exposome, refers to the collection of an individual’s exposures to infectious agents. A disease-specific infectome, based on the experimental approaches, can be employed from the “immunome” project as well as the “microbiome” projects. There is a concept in which the human body is a superorganism where the microbiome is part of the whole organism, as can be seen with mitochondria that existed as microbes prior to becoming organelles in eukaryotic cells of multicellular organisms over time. A similar argument can now be made in regard to normal intestinal flora, living in symbiosis within the host.

We Are All on Drugs

The human microbiome manufactures dozens of drug-like compounds in large quantities.

Surveying the genes in the human microbiome has led to the discovery of different compounds with potent cell-killing, antibiotic and immune-modulating activities. The microbiome’s ability to synthesize so many drug-like molecules could help explain idiosyncratic responses people often have to man-made chemicals. It is like we are all taking 10 to 12 prescriptions, but in each of us these prescriptions are unique and not the same as within others.

Medications have been developed from natural products. The most famous is the development of penicillin. Many complex drug molecules are microbial products as well (see Figure 5).

Therapy Collagen-induced Arthritis

Treating collagen-induced arthritis, a mouse model for chronic arthritis by introducing a single strain of bacteria into the animals’ guts, reduced disease incidence and severity.

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The specificity of these outcomes suggests that simply eating a few servings of yogurt to provide a general boost to the gut microbiome may not be nearly as effective as delivering a particular species to a particular patient. “There may be quite a bit of difference between mucking around with the microbiome and giving probiotics. They’re not the same thing,” Murray says. Instead, he advocates thinking about microbial treatments as “brugs,” or bacterial drugs. Probiotics have been shown to improve rheumatoid arthritis but only in a small number of patients.\(^{(9)}\)

A perturbed intestinal microbiome has been associated with an increasing number of gastrointestinal and non-gastrointestinal diseases including Clostridium difficile infection (CDI). It has become recognized that fecal microbiota transplantation (FMT) can correct the dysbiosis that characterizes chronic CDI, and effect a seemingly safe, relatively inexpensive, and rapidly effective cure in the vast majority of patients so treated.\(^{(18)}\)

Diet

Microbiologists have known for some time that different diets create different gut flora, but previous research has focused on mice instead of humans, leaving the actual relationship between our food and our stomach bacteria unclear. A diet study indicates that these changes can happen incredibly fast in the human gut – within three or four days of a big shift in what you eat.\(^{(19)}\)

The bacteria that lives in peoples’ guts is surprisingly responsive to change in diet. A short-term diet composed entirely of animal or plant products alters microbial community structure and overwhelms inter-individual differences in microbial gene expression. Microbial activity mirrored differences between herbivorous and carnivorous mammals, reflecting trade-offs between carbohydrate and protein fermentation. Foodborne microbes from both diets transiently colonized the gut, including bacteria, fungi and even viruses. Finally, increases in the abundance and on the animal-based diet support a link between dietary fat, bile acids and the outgrowth of microorganisms capable of triggering inflammatory bowel disease.

Lactobacillus casei 01 supplementation improved the disease activity and inflammatory status of patients with RA. This needs to be followed up, because a simple addition to diet may not be the answer.\(^{(20)}\)

There was not just a variation in the abundance of different kinds of bacteria, but in the kinds of genes they are expressing. The functional effects of commensal bacteria on T helper cell differentiation have led to the emerging concept that microbiota composition determines T effector- and T regulatory-cell balance, immune responsiveness and homeostasis.\(^{(21)}\) The term “genetic dysbiosis” highlights the role of human genetic variants affecting microbial recognition and host response in creating an environment conducive to changes in the normal microbiota and its relation to disease.\(^{(22)}\)

Surgery

Peter S. Stefano studied obese patients after gastric bypass surgery, which causes dramatic weight loss and often resolves obesity-induced type 2 diabetes.\(^{(11)}\) There were major changes in the patients’ intestinal microbiomes after the surgery. The researchers also compared the microbiomes of lean and obese individuals, and found dozens of species that overlapped between healthy lean people and the gastric bypass patients who showed the most metabolic improvement. Therefore, it can be deduced that successful gastric bypass patients develop the intestinal microbiomes of lean people.\(^{(11)}\) This suggests that the change may have been in part from the diet that was subsequent to the bypass. Diabetes also resolved in the patients.

Summary

1. In the microbiome, there are more microbes than cells in our body.
2. We have usually studied the effect of single organisms, but in the world of the microbiome there are many organisms acting in concert to either help our body or – if misdirected – injure our body.
3. We often can’t grow most of the inhabitants of the microbiome, perhaps because we cannot readily reproduce the environment in which they grow.
4. We need to recognize in health and disease that the microbiome is like a separate “organ” that is involved in the way our body responds to external influences and is important for our health and our immunity.
5. The microbiome is like a jungle inhabited by thousands of creatures that actually work in concert together to make their presence known.
6. The microbiome has a major impact on immunity and our understanding of it is rapidly expanding.
7. Alteration of the microbiome will be a new way to medically intervene in immune-mediated illnesses.
8. The microbiome can also be very helpful to our health.
9. Immune regulation through manipulation of the microbiome certainly has a future for potential therapy.
References


IgG4-related disease (IgG4-RD) is a recently recognized fibro-inflammatory condition that affects multiple organ systems with a consistent set of pathological features. This systemic disease is an excellent mimicker of malignancy, infections and other systemic immune-mediated conditions. While the etiology of IgG4-RD remains unknown, multiple features suggest the participation of unique immunological mechanisms including: significant elevation of serum IgG4; increased number of tissue-infiltrating IgG4-bearing plasma cells and dramatic clinical response to glucocorticoid therapy. Awareness about this condition can lead to prompt diagnosis and treatment and save patients from organ damage and unnecessary complications.

The concept of IgG4-related disease (IgG4-RD) was recognized in the first decade of this century(1) and has grown substantially in the past few years. The disease was first identified in the pancreas as a sclerosing and inflammatory condition of the gland, out of which emerged the entity of ‘Autoimmune Pancreatitis.’(2) In 2001, Autoimmune pancreatitis (AIP) was linked to elevated serum IgG4 concentrations (3), and soon after, an increased number of IgG4+ plasma cells in the pancreatic tissue became the hallmark of the disease.

Just two years later, clinicians taking care of patients with AIP observed a variety of extrapancreatic lesions in these patients and identified a unique histopathology in all the affected organs.(1) In the next few years the disease spectrum and list of involved organs expanded remarkably. IgG4-RD has now been reported to affect virtually every organ system, most commonly the pancreas, biliary tract, salivary glands, orbital tissues (the lacrimal gland and retro-orbital space), kidneys, lungs, lymph nodes, meninges, aorta, retroperitoneum, breast, prostate, thyroid gland, pericardium and skin.(4, 5) These organs can be involved either simultaneously or metachronously, generally over a period of years.

Recognition of IgG4-RD has grown remarkably and extended to specific disease entities across most medical specialties, yet most practitioners are probably still unaware of this disease spectrum. A broader understanding of the kinds of organs involved by IgG4-RD has led to the realization that many medical conditions previously viewed as separate conditions are actually part of the IgG4-RD spectrum. A list of clinical entities under the umbrella of IgG4-RD that were viewed as unique conditions in the past is shown in Table 1.

Since the disease recognition, in the past decade more than a dozen names have been used to designate this condition (see Table 2). In 2011, investigators agreed that “IgG4-related disease” is the most appropriate name for this condition, given the current state of knowledge regarding the disease.(6) This decision was supported by the organizing committee of the 2011 International Symposium on IgG4-RD.
Patients affected with this condition are initially misdiagnosed as having cancer, infection or another immune-mediated condition and are usually cared for and followed by multiple specialties. Lack of a systemic approach has led to the under recognition of this disease.

**Epidemiology**

The overall epidemiology of IgG4-RD in the general population remains unknown. Most of the epidemiological data in the literature is from cohorts of AIP and mostly from Japan. The total number of patients with IgG4-RD in Japan in 2009 was approximately 8,000 based on a nationwide survey that estimated a prevalence rate of 6.3 per 100,000 population.\(^7\)

This condition usually affects elderly men with a mean age between 58 and 69. The male to female ratio is reported 4:1\(^8\), which is surprising and unique for an autoimmune disease. Studies of patients with only head and neck involvement of IgG4-RD show almost equal sex distributions, indicating specific tendency for different organ involvements in different sexes.\(^7\)

IgG4-RD was initially recognized in Japan, and most studies reported in the literature are from Asia. As knowledge spread to the investigators and clinicians around the world, it seems that the disease occurs in every geographic and ethnic population with no obvious preference. Definitive assessment of its incidence and prevalence among all populations as a systemic disease requires multinational cohorts studying IgG4-RD, which are lacking at this point.

**Clinical Manifestations**

The initial presentation of IgG4-RD is often a mass that has developed subacutely in the affected organ, causing symptoms due to mass effect or damage to the organ (eg, painless jaundice due to a mass or swelling in the head of pancreas, pseudotumor of the orbit or a pulmonary nodule resembling cancer). Multiple organ involvement is reported in 60 percent to 90 percent of the patients, but may not all be symptomatic at diagnosis.

Patients rarely manifest constitutional symptoms of fever or weight loss. A history of asthma, eczema or atopy is commonly

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**Table 2**

Various names used in the medical literature to designate IgG4-related disease

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<td>IgG4-related disease</td>
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<td>IgG4-related systemic sclerosing disease</td>
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<td>IgG4-related autoimmune disease</td>
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<tr>
<td>Hyper-IgG4 disease</td>
</tr>
<tr>
<td>IgG4-positive multiorgan lymphoproliferative syndrome</td>
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<tr>
<td>Systemic IgG4-related plasmacytic syndrome</td>
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<td>IgG4 syndrome</td>
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Figure 1: 40-year-old Caucasian woman with bilateral enlargement of submandibular glands due to IgG4-related sialadenitis

Figure 2: 47-year-old African-American woman with IgG4-related dacryoadenitis

Figure 3: Histopathology (A and B) and immunohistochemical analyses (C and D) of the lacrimal gland of a patient with IgG4-RD, showing storiform fibrosis (A) and dense lymphoplasmacytic infiltrate and scattered eosinophils (stained with hematoxylin and eosin) (B). Immunohistochemical staining showed many IgG + plasma cells (C), most of those are IgG4 + plasma cell (D). The ratio of IgG4 to IgG cells is 0.9.

Figure 4: Significant steroid responsiveness of IgG4-related cholangitis evident in ERCP imaging prior and post treatment
reported. Forty percent of patients with IgG4-RD have lymphadenopathy at the time of their presentation.

Serum inflammatory markers such as the erythrocyte sedimentation rate and C-reactive protein are usually modestly elevated. Increased levels of serum IgE and peripheral eosinophilia can be found in some patients. Antinuclear antibody (ANA) assays and rheumatoid factors are positive in more than half of all patients with IgG4-RD, but specific extractable nuclear antigen autoantibodies such as anti-Ro/SSA and La/SSB are absent. Many patients with IgG4-RD have hypocomplementemia. Several autoantibodies, both specific and nonspecific to the pancreas, have been identified in AIP. However, none of them has been validated as a diagnostic marker for AIP.\(^{(9)}\)

Patients with IgG4-RD usually have elevations of serum IgG4 concentrations up to 40 times the upper limit of normal.\(^{(10)}\) The reported sensitivities of elevated serum IgG4 concentrations for the diagnosis of IgG4-RD vary generally from 68 percent to 95 percent.\(^{(11)}\) Although issues with accurate measurement of serum IgG4 concentration like prozone phenomenon can explain part of this variability, cumulative literature suggests that serum IgG4 concentration is not a reliable biomarker for diagnosis and disease activity monitoring in IgG4-RD. Patients who have multiple organ involvement tend to have higher serum IgG4 concentration, which could be helpful, but lack of serum elevation in a patient with one or two organ(s) involved is not unusual.

**Organ Involvement**

IgG4-RD can involve almost any organ system. The relative frequency of different organ involvements are not accurately reported because most of the cohorts studying this condition were designed to study a certain organ-specific index illness.

Based on one study looking at 114 patients with IgG4-RD in Japan,\(^{(13)}\) the most commonly affected organs are: liver and bile ducts (38 percent), salivary glands (34 percent), lung and pleura (26 percent), pancreas (24 percent), lacrimal glands (12 percent), retroperitoneum (11 percent), kidney (9 percent), aorta (9 percent) and gallbladder (8 percent). These frequencies may vary slightly in different studies, but these organs are among the most commonly involved organs in IgG4-RD.

**Most Common Organs Involved in IgG4-RD**

**Salivary glands.** Sialadenitis is one of the most common manifestations of IgG4-RD in general. Submandibular gland involvement frequently presents as unilateral or bilateral masses in the neck, which are usually mistaken as neoplasm [Fig 1]. Biopsy of the glands is usually interpreted as chronic sclerosing sialadenitis or Kuttner’s tumor, which is now regarded as IgG4-related sialadenitis.\(^{(14)}\)

It is essential to recognize this manifestation and make the right diagnosis, because many of these patients already have or will subsequently develop other organ involvements.

The parotid glands are sometimes involved either alone or together with the submandibular glands. Mikulicz’s disease was first reported in 1888 and is defined by bilateral, symmetrical, painless swelling of the lacrimal and salivary (parotid and submandibular) glands (Mikulicz 1888). This condition was later reported to be a variant of Sjogren’s syndrome.\(^{(15)}\) While a minor proportion of patients with constellation of these clinical symptoms who also have sicca symptoms and presence of SSA and SSB autoantibodies are diagnosed with Sjogren’s syndrome, the majorities have the diagnosis of IgG4-RD.

Patients with IgG4-related sialadenitis and dacryoadenitis usually present because of gland enlargement. They have minimal sicca symptoms unless presenting in the late stages of the disease with glandular damage and fibrosis. Although ANA is positive in 40 percent to 60 percent of patients with IgG4-RD, presence of autoantibodies to SSA and SSB is not a feature of this condition.

**Orbital Tissue.** Accumulating evidence supports that most inflammatory conditions regarded as “idiopathic orbital inflammation” (IOI) are actually ophthalmic manifestations of IgG4-RD.\(^{(16)}\) This disease may involve either a single anatomic structure or multiple structures within the orbit. The lacrimal gland is the most common orbital site affected by IgG4-RD\(^{(17)}\) [Fig2]. Other than dacryoadenitis, orbital myositis\(^{(18)}\), inflammatory pseudotumors involving the orbital soft tissue and sometimes extension to sinuses and facial cavities and nasolacrimal duct involvement are features of this disease.

**Pancreas.** IgG4-RD was initially identified in the pancreas as autoimmune pancreatitis (AIP). This term now describes two different immune-mediated diseases in the pancreas. AIP type 1 is the pancreatic involvement of the IgG4-RD that is defined by lymphoplasmacytic sclerosing pancreatitis, in contrast to AIP type 2 characterized by granulocytic epithelial lesions.

Patients with type 1 AIP or IgG4-related pancreatitis usually present with painless jaundice, weight loss and mild abdominal discomfort. Acute pancreatitis is the presenting symptoms in only 3 percent of cases of AIP. These symptoms lead clinicians to suspect the diagnosis of pancreatic cancer rather than pancreatitis. For this reason, AIP is diagnosed many times in patients who had already undergone Whipple procedure for pancreatic cancer. The classic radiologic findings in AIP include either a diffusely swollen sausage-shaped pancreas or a localized mass.

Fortunately the understanding about this condition has grown substantially, and diagnostic criteria have been created for AIP. Nowadays, the diagnosis is mostly made on the basis of radiologic findings and serology (elevated serum IgG4 level) and is usually confirmed by needle biopsy via endoscopic retrograde cholangiopancreatogram (ERCP), sparing these patients from complicated Whipple surgery.
Liver and Bile Ducts. IgG4-related sclerosing cholangitis is the most common presentation of the disease in the liver that resembles primary sclerosing cholangitis significantly except for the response to treatment [Fig 3]. These patients can be treated successfully with steroids and avoid fast progression to cirrhosis with appropriate diagnosis.

Inflammatory pseudotumors of the liver, IgG4-related hepatitis and acalculous lymphoplasmacytic cholecystitis are other IgG4-RD manifestations in the liver.

Lungs. Pulmonary involvement of IgG4-RD is a common manifestation in this systemic condition. Many patients are either asymptomatic or have chronic respiratory symptoms while the work-up reveals lungs nodules, ground glass opacities, alveolar/interstitial inflammation, bronchovascular bundle thickening or pleural thickening and effusion. Large airway disease causing tracheobronchial stenosis has been reported in IgG4-RD.

Aorta. IgG4-RD accounts for a significant proportion of inflammatory aortitis, both in the thoracic(19) and abdominal aorta. In many cases described as chronic sclerosing aortitis or isolated aortitis, the true diagnosis is IgG4-RD. IgG4-related aortitis is one of the most critical manifestations of IgG4-RD and requires immediate treatment to prevent fatal complications, including ruptured aortic aneurysm.(20)

Kidney. The clinical manifestations of IgG4-RD in the kidney consist of hematuria, proteinuria, decreased kidney function and various radiologic findings including diffuse renal enlargement, focal renal masses and thickening of the renal pelvis. Kidney lesions are mostly found in association with other organ involvement. IgG4-related tubulointerstitial nephritis (TIN) is the most common histology pattern of the kidney involvement. Cases of membranous glomerulonephritis have been described in this population, but whether it is secondary to immune complex deposition or due to the disease inflammatory process is not clear.

Retroperitoneum. More than half of the idiopathic retroperitoneal fibrosis cases have shown typical histologic findings for diagnosis of IgG4-RD in several studies. Histology confirmation for IgG4-RD is usually challenging in these cases because of the advanced stages of fibrosis, when these lesions become symptomatic leading to biopsy as well as limited tissue through core needle procedures.

Lymph node. Lymphadenopathy is a common finding in patients with IgG4-RD and mostly is reported in association with other organ involvements. Generalized lymphadenopathy as an initial sole presentation of IgG4-RD is possible but can be a challenging diagnosis. The disease in lymph nodes does not cause storiform fibrosis. Lack of typical histology features makes it difficult to differentiate IgG4-related lymphadenopathy from other conditions associated with elevated IgG4, including multicentric Castleman disease and malignancies including lymphoma, infections and sarcoidosis.
Making the diagnosis of IgG4-RD purely on the basis of lymph node pathology is not recommended. Many of these patients develop other organ involvement over time, which confirms the diagnosis.

**Other Organ Involvement.** Riedel’s thyroiditis as part of multifocal fibrosclerosis syndrome has been described to be a thyroid manifestation of IgG4-RD. Idiopathic pachymeningitis, hypophysitis, perineuritis, pericarditis, prostatitis and mastitis are among other manifestation of this condition.

**Pathology**

IgG4-RD is similar in many ways to sarcoidosis, another systemic disease that affects virtually all organ systems, defined by a distinctive histologic features regardless of the organ involved. Dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phelebitis are the three major histologic features of this condition (Fig. 4). Tissue eosinophilia is another common finding in most cases.

Presence of such histology in combination with positive staining for IgG4 plasma cells is the gold standard of the diagnosis. Specific criteria for the cut-off number for IgG4-bearing plasma cells in different organs has been suggested, and it could be helpful to the pathologist to call the staining positive.

Pathologic features that exclude the diagnosis of IgG4-RD are the presence of granulomas, giant cells and neutrophilic microabscesses. Prominent neutrophilic infiltrates and areas of necrosis are not usually seen in this condition.

**Treatment**

One of the characteristics that distinguishes IgG4-RD from its mimickers is its dramatic response to glucocorticoid treatment. Steroid responsiveness has been used in the clinical diagnostic criteria for AIP. Prompt improvement following the initiation of glucocorticoid always happens, provided the therapy is initiated prior to the organ damage or before the fibroinflammatory process becomes densely sclerotic.

There has been no prospective randomized control trial for treatment of AIP or IgG4-RD. The best data supporting all treatment approaches is based on retrospective observational studies and case series in the field. Japanese guidelines based on expert opinion and literature evidence suggests glucocorticoid treatment as the cornerstone of initial therapy.

Because of significant increase in relapse rate after tapering the steroid, different disease-modifying antirheumatic drugs (DMARDs) have been used for management of IgG4-RD. Multiple studies showed no clinical significant improvement and lack of ability to taper steroids with usual conventional DMARDs, including 6-mercaptopurine, azathioprine, methotrexate and mycophenolate mofetil.

On the other hand, case series and recent clinical trial of B-cell depletion with rituximab showed promising results, with complete improvement of patients’ symptoms and ability to discontinue steroids.

**Conclusion**

IgG4-RD is a recently recognized condition with pathological features that are consistent across a wide range of organ systems. This condition unifies a large number of medical disorders previously regarded as idiopathic conditions or single-organ diseases.

It is a protean condition mimicking many rheumatologic disorders, infection or malignancies. Clinician’s awareness about this condition and prompt diagnosis can spare many patients from unnecessary surgeries and organ failures.

There still remain many unknowns about the etiology of IgG4-RD. Ongoing clinical and immunologic investigations into the nature of IgG4-RD should provide more information about the immunopathogenesis and clinical course of the disease.

**References:**


Giant Cell Arteritis (GCA), or Temporal Arteritis, is the most common primary vasculitis. The disease is characterized by inflammation of the large and medium-sized vessels, predominately favoring the branches of the proximal aorta.

**Epidemiology**

GCA is a disease that typically occurs in people older than 50 years old, with a peak incidence in the seventh decade of life. GCA appears to be more common in Caucasians of Northern European descent.\(^{1, 2, 3}\)

A study looking at the incidence of GCA in Shelby County, Tenn., revealed a decreased incidence in African Americans compared to Caucasians.\(^{4}\) The reported incidence in areas of southern Europe, Asia and North Africa was lower. Women appear to be affected more than men at a ratio of 3:1.\(^{1, 2, 3}\)

**Pathogenesis**

Experimental evidence supports a major role of a T-cell mediated process in the pathogenesis of GCA. Dendritic cells (DCs), located in the adventitia of medium and large-
sized vessels, are activated via Toll-Like Receptor binding by specific ligands (including those resulting from infective agents).

These activated DCs, via release of chemokines, lead to recruitment and stimulation of CD4 T-cells and macrophages through the vasa vasorum into the vessel wall. These activated CD4 T-cells and macrophages then secrete pro-inflammatory cytokines. In particular, interactions between activated T-cells and the macrophages in the adventitia produce IL-1, IL-6 and Transforming Growth Factor beta, whereas in the media, they produce metalloproteinases and participate in oxidative damage. These factors then lead to fragmentation of the internal elastic lamina, intimal proliferation, thrombosis and possible vessel occlusion.(5, 6, 7 and 8)

Clinical Features

The clinical features of GCA could be broadly classified in two ways: those that are caused by systemic inflammation, and those that are a result of ischemia. Fevers, fatigue, weight loss, night sweats, Polymyalgia Rheumatica-like symptoms (pain and stiffness in the neck, shoulder/pelvic girdle area) and elevated acute phase reactants are common signs and symptoms that could be attributed to systemic inflammation. Peripheral synovitis can also occur, but usually less frequently. (9, 10, 11, 12 and 13)

When looking at the features that result from vascular injury, headaches have been shown to be the most common, being present in 90 percent of patients. The headaches are usually located in the temporal or occipital areas and may be associated with scalp tenderness. Jaw claudication is also common. (9, 10, 11, 12 and 13)

Ocular symptoms are feared complications of GCA. The most common ocular manifestation of GCA that leads to vision loss is Anterior Ischemic Optic Neuropathy (AION). AION results from occlusion of the posterior cilliary arteries. The vision loss is usually painless and acute. Amaurosis fugax and diplopia may precede the acute vision loss. Posterior Ischemic Optic Neuropathy and Central Retinal Artery Occlusion can also be seen. Fever, weight loss, jaw claudication, diplopia, transient visual loss and older age are predictors of worse visual prognosis. (9, 10, 11, 12 and 13)

Limb claudication, and the alteration of peripheral pulses stemming from large-vessel involvement, occurs in less than 20 percent of patients. Cough and hoarseness can be seen in less than 10 percent of patients. Other infrequent manifestations (<5 percent of patients) may include: peripheral neuropathy, tongue claudication, ischemia of the central nervous system, tissue necrosis, and deafness. (9, 10, 11, 12 and 13)

Diagnosis

The temporal artery biopsy (TAB) is the most useful tool for diagnosing GCA. A biopsy is usually attempted on the symptomatic side. A contralateral biopsy, however, may be warranted in patients with a high suspicion for GCA and a negative, initial TAB. Given the potential focal positioning of the inflammatory infiltrate, it is important to obtain a sufficient sample of the temporal artery. Studies have shown that biopsy lengths of 0.5cm to 3cm are adequate for histologic analysis.(12)

The stereotypic histologic morphology of GCA is a “panarteritis” or transmural inflammation of the vascular wall. The elastic lamina may be fragmented. In more chronic disease, intimal hyperplasia may cause arterial lumen occlusion. (12)

Laboratory data are also very useful in the diagnosis of GCA. The erythrocyte sedimentation rate (ESR) and C-reactive protein are usually elevated. Weyand et al. noted that 25 percent of patients with positive temporal artery biopsies had normal ESRS prior to the initiation of glucocorticoids. Anemia and thrombocytosis can also be seen. (13)

Imaging modalities, such as, ultrasound (US), magnetic resonance angiography (MRA), and computed tomography
angiography (CTA) have been studied. Early inflammatory changes in the superficial branches of the aortic arch can be visualized with ultrasonography, while MRA and CTA are more useful in evaluating the thoracic and abdominal aorta.

Treatment

Glucocorticoids have been the mainstay of treatment for GCA. Typically, in patients without end-organ damage, prednisone is initiated at 1mg/kg/day. The dose is then usually titrated down, only when a patient’s symptoms and inflammatory markers have normalized. Mazlumzadeh et al. were able to show that patients who received “pulse dose” intravenous steroids (15mg/kg of ideal body weight per day) tended to experience increased frequencies of sustained remission after treatment compared to patients who received a standard dose of 40mg/day of prednisone. In addition, over time, the patients who received the pulse-dose steroids were able to more rapidly taper their oral prednisone dose.(15)

In an attempt to mitigate the various short-term and long-term complications of glucocorticoids, several trials utilizing various disease-modifying drugs have been performed. Unfortunately, trials using methotrexate, infliximab, adalimumab and etanercept were unable to show any glucocorticoid sparing effect.(16)

Recently, interest has been shown in the humanized monoclonal antibody to IL-6 receptor, tocilizumab. Several case reports, as well as a case series reported by Unizony, et al., revealed promising clinical results. Long-term, randomized-control trials are currently in planning.(17)

Retrospective reviews have shown the benefits of low-dose aspirin therapy in GCA, including the potential decrease in risk of ischemic events and vision loss. Appropriate bone protective measures should be taken with glucocorticoid treatment.(16)

Prognosis

Despite treatment, 60 percent of patients will experience disease relapse.(17) Vigilant monitoring of clinical signs and symptoms is needed to prevent long-term complications.

BIBLIOGRAPHY

Rheumatoid Arthritis (RA) is the prototypical autoimmune arthritis. It’s a rheumatologic illness with the most immune targeted therapies.

In the late 1990s, TNF inhibitors were introduced and marked the advent of targeted biologic therapy for RA. The evolution of therapy for rheumatoid arthritis has been from symptomatic treatment to relatively unfocused disease modifying anti-rheumatic (DMARD) therapy, and presently to biologic and small molecule therapies that target particular proteins important in the inflammatory process.

As understanding of the immune process has improved, so have the tools for treatment, diagnosis and monitoring. The 1987 American College of Rheumatology (ACR) criteria uses the Rheumatoid Factor (RF) and Erythrocyte Sedimentation Rate (ESR) lab tests to help diagnose RA. The 2010 EULAR/ACR Criteria added tests for C-reactive protein (CRP) and anticitrullinated peptide / protein antibodies.

Anticitrullinated peptides/protein antibodies can be present years before the onset of arthritis, and they have been demonstrated to have a high diagnostic specificity and a high positive predictive value for RA. Understanding of citrulline immunity could ultimately lead to new therapies and possibly prevention of RA.

Differences in immune response to stress may help in understanding rheumatologic conditions. For instance, patients with RA have been shown to have higher stress-induced levels of IL-1b and IL-2 compared to patients with psoriasis and healthy controls. It has been shown that cell immunity associated with cytomegalovirus (CMV) exposure influences the clinical response to DMARD therapy in RA. The suggestion is that changes in T-cell immunity mediated by viral persistence may affect treatment response and possibly outcomes in RA.

The advent of anti-TNF therapy brought on the renaissance of rheumatology; however, anti-TNF therapy can unexpectedly trigger the onset or exacerbate multiple sclerosis (MS). This is thought to be related to the balance of regulatory T-cells (Tregs) and effector T-cells (Teffs). A better understanding these differential effects of TNF on Teffs and Tregs may lead to safer and more effective anti-TNF therapies.

RA is considered to be a complex genetic disease characterized by environmental triggers. New insights from DNA sequence-based analysis of gut microbial communities suggest a possible role for the microbiota in the pathogenesis of RA. It has been proposed that the step beyond therapy is to induce immune tolerance in the treatment of rheumatoid arthritis.

More confident diagnoses and better understanding of the immune process have led to more effective therapies and allowed the opportunity to tailor therapy in such a way as to achieve low disease activity, commonly referred to as Treat to Target. Years ago we referred to our therapies as remittive; however, they were more properly Disease Modifying. Clearly, our goal is to attain 100 percent improvement; however, until we can reach that goal, we will strive for the greatest improvement.

It is clear that immune modulation can in some cases place patients in a clinical remission; however, combined therapy with biologic response modifiers has resulted in unacceptable side effects. At this juncture a combination of a conventional DMARD therapy with a Biologic Response Modifier seems to give the best opportunity to preserve joint architecture in this chronic inflammatory erosive arthritis. It is exciting to be on the cusp of real understanding and meaningful therapies for one of the most disabling medical conditions.

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Lupus is a systemic disease known to Western medicine for over 1,000 years. It was named for the characteristic facial rash, often scarring, noted to favor markings on the snout of the European wolf. In the mid to late 1800s, this illness was clearly associated with systemic disease featuring lymphadenitis, arthritis, altered mental status, chest pain and kidney disease.

We now know that the underlying lesion of lupus is derangement of the immune system with chronic inflammatory tissue destruction. Our goal is to explore the nature of systemic lupus Erythematosus (SLE) and discover new insights and strategies currently in practice as well as in the research pipeline.

There are genetic and environmental factors responsible for expression of pathology leading to manifestation of the clinical complex known as SLE. The role of major histocompatibility complexes (MHCs) and autoimmunity has been the subject of intense research since the 1970s. MHC class II was discovered to be the source of autoantibody coding. Although the variants HLA-DR2 and HLA-DR3 most consistently correlated with autoimmune disease, reliable development of gene assays failed to yield diagnostic predictability as economical or helpful as the auto antibodies products. This is likely due to posttranslational folding as well as variations in DNA transcription to Micro RNA fragments.

Environmental triggers in the form of viral, bacterial and fungal infection may lead to antibody/antigen complexes, complement activation and cytokine release. Presentation of antigen, including self-made immune complex fragments, to T-cells result in amplification and perpetuation of immune response. In lupus, this can become the “new” normal that leads to chronic multi-organ system autoimmune attack and target specific tissue degradation.

When this process is prolonged, there is depletion of vital complement and susceptibility to infection. Watch out for a rise in C-reactive protein. This can be released disproportionately with infection and activate the classic complement pathway. Fever has long been cited as a feature of connective tissue disease in general and SLE in particular. In my experience, fever as a presenting symptom of lupus is not common. Many times there is tissue inflammation or damage from chronic connective tissue disease activity, but fever is usually an end-stage response and the underlying damage is not difficult to uncover. When a significant fever is observed, it would be wise to assess for infection or drug reaction. (Too often immunogenic drugs like Trimethoprim/Sulfamethoxazole, Hy-
dralazine, estrogen-based hormones and some of the older anti-arrhythmic, anti-hypertensive drugs may be the putative agents.)

A disrupted immune system goes down in a certain order: insidious at onset, there is chronic damage by neutrophils and macrophages with release of cytokines and proteolytic enzymes. In the setting of fulminant lupus flare, the adaptive immune system goes into overdrive, activating B-cells and T-cells that amplify the immune response, recruiting an assortment of immune cells to arm and deploy a wide array of cytotoxic weaponry. When vascular beds and homeostatic organ tissue becomes injured, the downward spiral begins and often continues even in the setting of effective treatment.

Criteria to classify SLE for clinical trials have been developed. Keep in mind these are not diagnostic criteria. We use these as a guide to diagnosis.

Clinical and immunologic criteria used in the SLICC classification system*(10)

**Clinical Criteria**

(1) Acute Cutaneous Lupus OR Subacute Cutaneous Lupus
- Acute cutaneous lupus: lupus malar rash (do not count if malar discoid), bullous lupus, toxic epidermal necrolysis variant of SLE, maculopapular lupus rash, photosensitive lupus rash (in the absence of dermatomyositis)
- Subacute cutaneous lupus: non-indurated psoriaform and/or annular polycyclic lesions that resolve without scarring, although occasionally with post-inflammatory depigmentation or telangiectasia

(2) Chronic Cutaneous Lupus
- Classic discoid rash localized (above the neck) or generalized (above and below the neck), hypertrophic ( verrucous) lupus, lupus panniculitis (profundus), mucosal lupus, lupus erythematosus tumidus, chilblains lupus, discoid lupus/lichen planus overlap syndrome

(3) Oral Ulcers OR Nasal Ulcers
- Oral: palate, buccal, tongue
- Nasal ulcers
- Be sure to document the absence of other causes, such as vasculitis, Behcet’s disease, infection (herpesvirus), inflammatory bowel disease, reactive arthritis and acidic foods

(4) Non-scarring alopecia
- Diffuse thinning or hair fragility with visible broken hairs, in the absence of other causes such as alopecia areata, drugs, iron deficiency and androgenic alopecia

(5) Synovitis involving two or more joints
- Characterized by swelling or effusion
- OR tenderness in two or more joints and at least 30 minutes of morning stiffness

(6) Serositis
- Typical pleurisy for more than one day OR pleural effusions OR pleural rub
- Typical pericardial pain (pain with recumbency improved by sitting forward) for more than 1 day OR pericardial effusion OR pericardial rub OR pericarditis by electrocardiography
- In the absence of other causes, such as infection, uremia and Dressler’s pericarditis

(7) Renal
- Urine protein–to-creatinine ratio (or 24-hour urine protein) representing 500 mg protein/24 hours OR red blood cell casts

(8) Neurologic
- Seizures, psychosis, mononeuritis multiplex (in the absence of other known causes such as primary vasculitis), myelitis, peripheral or cranial neuropathy (in the absence of other known causes such as primary vasculitis, infection and diabetes mellitus), acute confusional state (in the absence of other causes, including toxic/metabolic, uremia, drugs)

(9) Hemolytic anemia

(10) Leukopenia (<4000/mm3)

OR Lymphopenia (<1000/mm3)
- Leucopenia at least once: In the absence of other known causes such as Felty’s syndrome, drugs and portal hypertension
- Lymphopenia at least once: in the absence of other known causes such as corticosteroids, drugs and infection

(11) Thrombocytopenia (<100,000/mm3)
- At least once in the absence of other known causes
such as drugs, portal hypertension and thrombotic thrombocytopenic purpura

**Immunologic Criteria**

1. **ANA** level above laboratory reference range
2. **Anti-dsDNA** antibody level above laboratory reference range (or two-fold the reference range if tested by ELISA)
3. **Anti-Sm**: presence of antibody to Sm nuclear antigen
4. **Antiphospholipid antibody** positivity, as determined by
   - Positive test for lupus anticoagulant
   - False-positive test result for rapid plasma reagin
   - Medium- or high-titer anticardiolipin antibody level (IgA, IgG, or IgM)
   - Positive test result for anti–b2-glycoprotein I (IgA, IgG, or IgM)
5. **Low complement** (C3, C4, or CH50)
6. **Direct Coombs’ test** (in the absence of hemolytic anemia)

So how do we fight this war within ourselves? First, forewarned is forearmed. A thorough personal and family history followed by a careful physical examination is essential.

Obtain an ANA by immunofluorescence with extractable nuclear antigens, native (double stranded) DNA and a complement panel. The correct ANA test code to screen for ANA by immunofluorescence at QUEST is 38318 and LABCORP is 164947.

For further testing, there are test panels from clinical laboratories like, Quest Diagnostics, Labcorp, Exagen with the Avise SLE+CTD panel and RDL Reference Laboratory. Histologic studies of the skin, kidneys and other internal organs may be necessary.

The sooner lupus is identified, the less leverage must be brought to bear to combat it. Barring contra-indications, we often begin with NSAIDs, anti-malarial medications and low-dose corticosteroids. Lifestyle changes such as sun protection, a sensible healthy diet and regular exercise should be advised. Caution regarding use of immune offensive medications as listed above when considering birth control options, infectious, neuro-psychiatric, hypertensive and cardiac disease. Monitor patients closely for symptomatic as well as unsuspected flares or disease progression. Survey metabolic profiles, complete blood counts including platelets, urinalyses and acute phase reactants at baseline and at regular intervals.

Keep in mind, even quiescent lupus can flare after years’ long indolence to threaten major organs or vascular tissue. That’s why proper and effective management of the disease requires a team effort:

1. Educate Patients about Lupus. Encourage participation in local and national support groups.
2. Communicate with all treating physicians and make sure they have access to a rheumatologist (preferably one who knows the patient well).
3. List all medications from all providers.
4. Consult rheumatologist prior to all major and most minor surgeries.

A rheumatologist should always be consulted for treatment of refractory disease. The choice of medications for organ or life-threatening pathology is complicated and potentially toxic. Some options are FDA approved, while some are tried and true through years of experience.

There is no “typical” case of lupus. Every lupus sufferer’s disease is a little different from the rest. Over the past 20 years, we have come to recognize disparate vulnerability of some ethnic subgroups. The juvenile and senior population may also demonstrate a departure from the expected disease course.

Particular care should be taken when a patient with a history of lupus anticipates pregnancy or unintentionally becomes pregnant. Conventional experience holds that although female patients often do a little better during pregnancy, the gravid state can aggravate systemic manifestations. Again, close monitoring is essential, and a high-risk obstetrician should be consulted early on in the prenatal process. In the event of a major lupus flare, difficult decisions may become necessary for the immediate and long-term safety of the mother and baby.

Treatment options are still evolving, with epigenetic principles charting the course to

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**SLICC Classification Criteria for Systemic Lupus Erythematosus**

Requirements: ≥ 4 criteria (at least 1 clinical and 1 laboratory criteria)
OR biopsy-proven lupus nephritis with positive ANA or Anti-DNA

<table>
<thead>
<tr>
<th>Clinical Criteria</th>
<th>Immunologic Criteria</th>
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<tbody>
<tr>
<td>1. Acute Cutaneous Lupus*</td>
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<td>2. Anti-DNA</td>
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<td>3. Oral or nasal ulcers*</td>
<td>3. Anti-Sm</td>
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<td>4. Antiphospholipid Ab*</td>
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<td>7. Renal*</td>
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<td>8. Neurologic*</td>
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*SLICC: Systemic Lupus International Collaborating Clinics

†SLICC: Systemic Lupus International Collaborating Clinics

*See notes for criteria details

personalized therapies. Anti BlyS designer antibodies such as belimumab (Benlysta) and cytotoxic agents including azathioprine, methotrexate, mycophenolate mofetil and cyclophosphamide, are currently in use, as well as plasmapheresis in catastrophic vaso-occlusive disease (inflammatory vasculitis or obstructive antiphospholipid antibodies with limited inflammatory destructive quality).

This list is representative of our armamentarium, but by no means exhaustive. Belimumab is the first drug to be approved by the FDA for SLE in over 50 years and is the only biologic approved to treat lupus, but some of the other biologics available are used at times off label for certain clinical indications. Development of investigational Micro RNA modulators and manipulation of pro-inflammatory and anti-inflammatory cytokines are in the research pipeline of several pharmaceutical companies. Although the role of rheumatologists is often pivotal to managing SLE, the primary care physician and other subspecialists often play a crucial part in overall patient care.

In conclusion, SLE is a protean, chronic autoimmune connective tissue disease that can affect almost any organ in the human body. Our ability to detect, classify, anticipate pathology and modify the course of disease is growing exponentially. Treatment of the disease is an ongoing process that spans decades. Proper and effective management requires a team effort, including an educated, alert and engaged patient along with her support network, primary care provider, rheumatologist and an assortment of appropriate subspecialists. Although we look forward to the introduction of new agents, we must not forget the wealth of older agents that are often more economical and, in the right hands, predictable.

Bibliography
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5. Pro-Inflammatory and Anti Inflammatory Cytokines in Rheumatoid Arthritis Dinarello C. and Moldawer L.L.
The definition of biologics or biopharmaceuticals varies widely. In general, however, most agree that they differ from conventional pharmaceuticals by the way in which they are created.

Biologics are “built” by cell culture, particularly those used in the field of rheumatology, rather than as a construct of chemicals. According to the Oxford dictionary, a biopharmaceutical is “a biological macromolecule or cellular component, such as a blood product, used as a pharmaceutical.”1 The FDA defines biological products under section 351 of the Public Health Service Act as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein … or analogous product … applicable to the prevention, treatment or cure of a disease or condition of human beings.”2,3 Obviously from the expansive definition provided by the FDA, biologics encompass much more than most consider when referring to this group of pharmaceuticals.

For this discussion, we will focus more on biologics as large proteins that are grown in cell culture and utilized in the treatment of chronic disease states such as rheumatoid arthritis, psoriatic arthritis, psoriasis and lupus. Using this very limited definition of biologics, the first biologic approved to treat rheumatic disease was etanercept, which is a monoclonal fusion protein that binds tumor necrosis factor – (TNF). It was first approved in 1998.

By binding TNF etanercept (Enbrel) blocks this cytokine from interacting with its receptor on immune cells, thus decreasing the stimulation of these cells. This decrease in stimulation is key to turning down inflammation in rheumatoid arthritis. After etanercept was approved, “second-generation” biologics blocking TNF were developed and approved. These “second-generation” biologics are antibodies such as infliximab (Remicade) and adalimumab (Humira), which actually could bind TNF attached and unattached to its receptor.

This is important because these “second-generation” TNF inhibitors could more avidly bind cell-bound TNF and were irreversible. This distinction has led to differences in the efficacy of the “second-generation” biologics in diseases like Crohn’s disease, in which etanercept does not seem to be efficacious.

These “second-generation” biologics are not the same as biosimilars because they have different structures. Second-generation biologics were not and are not attempting...
to mimic the first-generation drug. This is important because we do not want biosimilars to actually have significant differences in efficacy. As most of you are aware, biosimilars could also be referred to as “generic” biologics. However, since biologics are complex large proteins, to refer to them as generic biologics oversimplifies the difficulties in making copies of the original. Not to suggest that the issues with generics are not complex as well, but the complexity with biosimilars have many additional layers.

Woodcock et. al reviewed the complexity of biosimilars in their 2007 perspective, comparing the complexity of biologics to conventional “small molecule drugs.” Unlike small molecule drugs, which have a chemical structure that can easily be assessed and compared to its original drug, biologics are large molecules that have an amino acid structure that later chemically organize into their secondary, tertiary and finally quaternary structures.

Variability at any of these levels could significantly affect the biologic activity of this drug class. With this level of structure, concerns arise with hydrogen bonds, sulfite bonds, glycosylation of proteins as well as additional processes such as deamination. At each stage of developing these proteins changes can occur, and these changes could potentially lead to significant variability in the function of the drugs.

These changes could also affect the immunogenicity of these drugs. Due to their large molecular structure, biologics can incite immune mediated responses. These responses can lead to severe reactions to drugs, as seen more often in chimeric biologics such as infliximab (which contains both mouse and human proteins) or decrease efficacy by increasing anti-drug antibodies that block the drug from working as well – effectively reducing the dose.

Another concern is that if pharmacists (as allowed by the ACA) can substitute without physician awareness from a trade name biologic to a biosimilar and vice versa, patients could develop immunogenicity that could range from decreased efficacy to life-threatening reactions. The physician would then need to recreate what happened to determine the cause of their patient’s lack of efficacy or reaction.

Because of these issues, the FDA is requiring trials to compare biosimilars to their trade name biologic. However, time of exclusivity will be extended only briefly if pharmaceutical companies study immunogenicity. This is unlikely to happen because the cost of the studies and potential negative impact of their results will cost the companies more than the year of exclusivity for their biosimilar.

The Patient Protection and Affordable Care Act passed in 2010 addresses in Section VII the issue of an approval pathway for biosimilar biologic products. In general, it addresses the processes that pharmaceutical companies must follow to receive FDA approval for a biosimilar. This document refers to biosimilars as having “no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product.”

Given the differences concerning biologics and biosimilars, we as physicians will have to push the FDA to remain vigilant about issues that could potentially harm our patients while at the same time balancing the desire to increase the availability of these novel drugs to more patients.

It’s no surprise that many biotechnology corporations are very interested in the establishment of specifics regarding biosimilars, particularly since many of them will stand to make large amounts of money if they are able to make acceptable biosimilars. In May 2014, some of the leading biotech news sites have been pleased by the FDA’s draft guidance regarding more biosimilars. Some of the terms that the FDA will be using are summarized in Table 1.

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<tr>
<th>Four Proposed Quality Assessments for Proposed Biosimilar Products</th>
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<td><strong>High Similar with Finger-print-like Similarity</strong></td>
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In summary, biologics have revolutionized the treatment of many chronic, disabling diseases but have been out of reach for many patients. The option of biosimilars will increase the availability, but as with all things, there are risks that we must consider. We must educate ourselves, our patients and our legislators on these issues.

References
The Affordable Care Act

By Helen K. Kelley

The Affordable Care Act (ACA), the national health reform law passed in 2010, was enacted with the purpose of providing new funding for public health and prevention, bolstering the healthcare and public health workforce and infrastructure, and fostering innovation and quality in healthcare. Reasons for the law included a high-uninsured rate, unsustainable healthcare spending, lack of emphasis on prevention of disease, poor health outcomes and health disparities across demographic lines.

In January this year, some provisions of the ACA went into effect that will bring about major changes for physicians. In an article published on Dec. 13, 2013, U.S. News and World Report stated that doctors should prepare themselves for three major changes in how they as a profession do business: a shift from private practice to medical networks, a full integration of electronic health records and changes in the healthcare payment model.

Atlanta Medicine recently spoke to two local physicians – Dr. Lisa Perry-Gilkes, chair of the Board of Directors of the Medical Association of Atlanta and in practice with Polaris Medical Group, and Dr. Thomas E. Bat, CEO of North Atlanta Primary Care – who shared their opinions and thoughts about these changes and how the Affordable Care Act has affected the way they do business.

How has ACA affected patients’ care?

Dr. Perry-Gilkes: As of now, it hasn’t had any effect on my practice at all. The changes that go with the ACA don’t impinge on what I do currently and haven’t affected my ability to care for patients. However, I don’t know what it will be like next year.

Dr. Bat: The ACA has caused many patients to experience increased stress due to concerns about costs of premiums, access to care and ability to continue seeing their doctors, as well as general confusion about whether or not the medications they are taking are covered. These patients need to sit down with a caring physician to discuss all these issues and to “re-establish” care, even though this is time-consuming for both physician and patient. Many patients with chronic debilitating diseases are struggling with this the most.

Simply finding out which physicians and health systems accept the new exchange patients is a challenge. Some patients who previously had commercial insurance and
have been “switched” to exchange plans are now finding they have to choose a primary care physician and make a visit just to get a referral to continue specialty care. This gatekeeper model has not always worked well in the past, but encouraging patients to have their own personal physician is a good thing.

**Has the State of Georgia’s political position toward ACA made a positive or negative impact?**

*Dr. Perry-Gilkes:* Honestly, I believe we missed out on an opportunity to have more people covered. About 60 percent of Georgia residents would have liked the Governor to go with the Affordable Care Act, but he didn’t.

The lack of providers is a real issue – in Georgia, we still have sick people who are not covered. You have to take into consideration the disparity between metro Atlanta and the rest of Georgia – there’s a big difference in the accessibility of care for people who live in or near a big city and people who live in rural areas. What the federation of medicine needs to do is try and find the happy medium between metropolitan and suburban and rural healthcare. There isn’t one shoe to fit all the problems, so it’s going to take some compromise.

It’s important that we, as physicians, let our patients and legislators know what we can do to make things better.

*Dr. Bat:* Our state leaders have looked at participation in the exchanges, accepting the Federal Exchange instead of building a state-based exchange. Considering all of the unclear issues and problems in the exchanges, this appears to have been a good decision. The exchanges have not functioned well, as the technology and the goals are not well defined by ACA.

The political decision to not expand Medicaid is a two-edged sword. Leaving federal money on the table that is especially needed in our rural health systems can be devastating. However, growing a payment system that does not work makes no sense. Our practice elected to start taking Medicaid again, as the government promised Medicare payment rates or parity two years ago. But the state has failed to process claims for Medicaid at the promised rates.

Medicaid patients are always a challenge due to their income, but many times they have accompanying educational and personal issues that create additional challenges. To not compensate providers for these challenges is a failed policy. Building and enlarging a failed policy will lead to a system that does not work for a greater percentage of our population. There are better ways to deal with the uninsured and poor; certainly block grants and healthcare vouchers are worth exploring.

**What suggestions would you make to improve ACA?**

*Dr. Perry-Gilkes:* I think we can find ways to improve access to healthcare. We’re going to have to come to a meeting of the minds to get all citizens of Georgia covered.

It’s not an insurmountable problem, but it’s going to take physician leaders and legislators working together to solve it. Healthcare is a “cornucopia” of challenges. If everyone would give a little, we can make a change.

*Dr. Bat:* I don’t think any one person can comprehend the challenges in this broad piece of legislation. A one-size-fits-all federal mentality does not work in a country as large and diverse as ours.

One of the impending parts of the ACA, referred to as the Independent Payment Advisory Board (IPAB), will be a disaster if implemented. The amount of analytics required to comply with the government’s guidelines for a Physician Quality Reporting System (PQRS) and Meaningful Use (MU) are making it virtually impossible to focus on patient care while documenting what the government requires.

Mandatory enrollment for individuals and employers has caused a great deal of grief in the political
world, yet we all need insurance. Encouraging our population to participate is a much better route than mandating coverage.

How has ACA affected your business?

Dr. Perry-Gilkes: Currently, it hasn’t affected my practice except for making changes to implement the electronic health record for patients. That’s had a significant impact.

And I wish the Medicaid plans we have in Georgia now were not so difficult to work with.

Dr. Bat: I think it’s too early to tell. As we move to “at-risk” population payment models, the more we do for our chronically ill patients, the worse our physician profiles will appear in government rankings. Of course, this will affect our pay and “bonuses.” We are exploring population-focused care models that are based on both capitation and fee-for-service, with bonus pools that include insurance companies, health systems and private IPAs.

Since we are currently a PCMH [patient-centered medical home] model, we believe population health is important, but the team serves one patient at a time to maximize outcomes. The newer compensation models will challenge us, because they see the “population” outcomes as more important than the “individual” outcomes. And, of course, all of this will be based on quality criteria that is truly reflective of economic data.

What do your physician colleagues think of ACA?

Dr. Perry-Gilkes: The majority of physicians I know are so busy taking care of patients that the ACA is still in the back of their minds. Nothing has really hit us yet – we’re still taking care of patients just as we have been for the past several years.

Other than the implementation of electronic medical records for patients, I haven’t seen anyone making major changes. No one’s losing any patients, and no one’s turning any patients down, either.

I don’t think the sky is falling, but it may be dipping a little bit. Doctors will always be here, and they will always care for patients. It just may not be done exactly the same way as in the past.

As healthcare providers, we have a lot of work to do – and one of our tasks is to help align the patient’s expectations and responsibilities when it comes to care.

Dr. Bat: Most of my physician friends are overwhelmed, just taking care of their patients. A busy physician is pulled in too many directions to become very involved in the political system. Physicians are hurt by constantly being referred to as the problem that needs to be fixed. America has the greatest healthcare in the world, and the use of statistics to suggest otherwise is disingenuous.

Unfortunately, this has allowed the government and large health systems to take over and profit from the confusion. Look at the recently released Medicare payment data: physicians received 7 percent of the nearly $1 trillion Medicare budget. That 7 percent includes all the medications, chemotherapy, vaccinations and tests that they perform in their offices. Diagnostic centers, labs and hospitals collect the remaining 93 percent of healthcare dollars. Yet physicians are portrayed as the bad guys.

It’s hard to be a doctor today, but fortunately for Americans we love what we do, and we will continue to work for the betterment of our patients.

Resources

The National Physicians Alliance, a national, multispecialty organization, has published a guide to key provisions in the Affordable Care Act that affect physicians. For more information, visit www.npalliance.org.

Medscape, a part of WebMD Health Professional Network, has content about the Affordable Care Act geared to healthcare professionals, including “8 Ways That the ACA is Affecting Doctors’ Incomes.” Go to www.medscape.com for more information.
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This Month’s Featured Board Members

Dimitri Cassimatis, MD

Dr. Cassimatis is Assistant Professor of Medicine at Emory University and Director of the Coronary Care Unit at Emory University Hospital Midtown. He divides his clinical time between Grady Memorial Hospital and Emory University Hospital Midtown. He is also co-director of the first year medical student cardiovascular pathophysiology module at Emory’s School of Medicine. Dr. Cassimatis received his MD from Harvard University and then spent 11 years in the United States Army before joining Emory in 2010.

Rutledge Forney, MD

Dr. Forney’s education includes an undergraduate degree from Duke University, Medical school at Emory University School of Medicine, Cum Laude, followed by an internship in Internal Medicine at Duke and a Dermatology Residency at University of California, San Francisco where she was Chief Resident of Dermatology. As a medical student, she spent 12 weeks studying skin cancer in Melbourne, Australia, and at the CDC in Atlanta. Dr. Forney founded Dermatology Affiliates in 2004. She is a Past-President of the Medical Association of Atlanta and past-President of the Atlanta Dermatological Association. Dr. Forney serves on the board of the Medical Association of Georgia and Medical Association of Atlanta and on the Board of Directors of the Women’s Dermatological Society. In addition, she is a fellow in the American Society of Laser Medicine and Surgery, a member of the American Medical Association, member of American Academy of Dermatology, member of the American Society for Dermatologic Surgery, and of the Georgia Society of Dermatologists.

John S. Harvey, MD

Dr. Harvey graduated from the University of Georgia with a B.S. Degree in Biochemistry prior to receiving an MD Degree from the Medical College of Georgia. Residency training at the University of South Florida Health Sciences University (USFHSU) in Tampa Florida was completed following a Chief Residency year in 1983. Dr. Harvey has been in the practice of general and trauma surgery for over 25 years. His private practice is in Alpharetta, GA and he is a trauma surgeon at the Gwinnett Medical Level II Trauma Center.

During his career Dr Harvey has served as Chief of Surgery and Chief of Staff at North Fulton Hospital in North Atlanta, and currently is Chief of Surgery at Gwinnett Medical Center. He has served as President of the Medical Association of Atlanta (MAA), and Speaker of the House of the Medical Association of Georgia (MAG). He currently remains on the MAA Board of Directors and the MAG Executive Committee.
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