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Medical Tourism

JOSEPH H. FRIEDMAN, MD
joseph_friedman@brown.edu

This column is about a different sort of medical tourism. The term “medical tourism” generally refers to patients who travel outside their country to seek medical care, usually because of expense. There are places that may be tourist destinations, with nice climates, beautiful beaches, cheap hotels and good food, where the staff may be first rate, often American- or European-trained, who practice medicine at a high level, with excellent nursing care, air-conditioned, hotel-like premises, and solicitous VIP treatment. The cost may be less than the co-pay for some insurance plans, or the treatment may not be covered by insurance in the U.S. or may be performed much sooner than can be provided by national insurers, as in Canada or England.

I have been a different kind of medical tourist. I spent time in Tanzania (3 months as a graduating medical student), working in or teaching in hospitals in Zambia (4 weeks), Kenya (2 weeks), Rwanda (10 weeks), Malawi (4 weeks) and Ghana (2 weeks). I cannot account for my focus on African countries, other than, perhaps, the fact that I have only gone to places where the national language, the language in which school is taught, medicine is taught and often communicated, is English. Unlike all of my African colleagues, I am monolingual, a major drawback, I believe, in life. I find the experiences always enriching. Now that I am an experienced, old-hand at this, or, simply, just old, and a professor at Brown, I have taken on the title of the visiting professor. Since I have visited places that are greatly deficient in neurology, I think I can make a difference, albeit a small one, in helping general internists understand and evaluate neurological problems better. There is, of course, a limit on how much one can accomplish in any period of time, and shorter, obviously, means less. However, some government ministries are loath to consider an expatriot for a stay of less than 2 or 3 months, assuming, correctly, I think, in most cases, that it takes several weeks for a newcomer to get his “sea legs.” It often takes some weeks to both understand English with a novel accent, especially when spoken softly, as is the norm in some places, and, perhaps more importantly for a teacher, to be understood.

When I was a Peace Corps teacher in Ghana, several decades ago, I sometimes would translate from English into English, for new American arrivals who were not understood by Ghanaians, or vice versa. Since then I have always taught at a slower pace, with attention to articulation, which might be wise advice for any teacher, especially one from New York.

There are two questions to consider about this type of medical tourism. What are the benefits for the tourist and what are the benefits for the recipient? The hosts always act grateful, although, to be honest, cultural insensitivity from both ends, may undercut this. My colleagues at home rarely appear to comprehend, however, how much the tourist receives in exchange.

Each medical trip I’ve made has always increased my gratefulness for being born when and where I was, for not being poor, for not having limited possibilities. But I’ve always been impressed with the resourcefulness of the local doctors, and for the patients’ tolerance of their limited medical possibilities. It is a harsh and awful fact that a family in most of Africa will accept as an unfortunate fate that they lack the money to pay for the tests or treatment for a loved one. It contrasts with the railing against the unfairness of fate I sometimes see from the children of the 88-year-old person with one of the dread neurological disorders of the elderly. Seeing medicine in different cultures teaches us about life, how each of us lives our lives as constrained by our cultures.

I do not believe that I have developed any greater insights than anyone else who visits a hospital for short periods. I am not an anthropologist, and, since I mostly have visited places only once,
I’ve, unfortunately, made no real friends to provide insights that I could not perceive on my own.

What the hosts get is extra education. In the places I’ve been there has been little neurology teaching available. There was one neurologist in Zambia, four in Ghana, one in Malawi, none in my area of Kenya. Neurological problems affect over a third of patients on the medical wards. If one learns neurology from someone who learned neurology from someone...who was not a neurologist, who did not know how to perform a neurological exam...you get the picture. I can help change that a little bit. Hopefully that makes a difference. I try to convey the excitement I feel about neurological disorders, perhaps inspiring someone to become a neurologist. It also brings a different teaching style than may be the norm. Some hospitals have preserved the pedantic style of the colonial UK, where professors were never wrong and certainly never to be challenged. Junior faculty are window dressing even when more knowledgeable than the senior doctor.

Cultural insensitivity may undermine the hosts’ feeling of gratefulness. This is usually due to the guest, but this has been rare, as best I can tell (but I am unlikely to be a sensitive guide, I admit). Some problems develop, I believe, from having too many ex-patriots, creating a two-tier system of doctors. The ex-pats become the “experts” and the nice guys, never disciplining the laggard students and house officers, while the local attending physicians are relegated to the shadows and to playing the “heavies.”

The experience is unparalleled. While this is a great experience that I recommend for doctors at all levels of practice, I am hopeful that poor countries can harness the expertise and attitudes of the increasing numbers of retired American physicians, who now have the time to continue making contributions they were unable to make before.

Author
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Dickensian Diagnostics: The Diseases of Christmas Past

What ailed Scrooge and Tiny Tim?

HERBERT RAKATANSKY, MD

When we first meet Ebenezer Scrooge (A Christmas Carol by Charles Dickens), he is miserable and friendless. He had been distanced from his father and sent to a boarding school. He was allowed to return home only at the urging of his sister, who reassured Scrooge, “Father is so much kinder than he used to be.” We are not told what happened at home and we know little else of his father (his mother is not mentioned) but it is not a stretch to conclude that Scrooge was emotionally deprived as a child.

His only sister, who was caring and for whom he cared, died in childbirth. He never forgave his nephew for this loss and was estranged from him.

A planned marriage was cancelled by his fiancée, discouraged by Scrooge’s total devotion to his business and making money. His only friend had been his business partner, Jacob Marley, who had a similar temperament, but was now deceased. His considerable wealth bought him neither comfort nor happiness. Scrooge lived very modestly and disavowed material pleasures.

If this all sounds authentic, it is. Dickens was brought up in poverty in London and knew of what he wrote.

Mr. Fezziwig, his first employer, was remembered as a caring and kind person. One might surmise that Dickens planted this memory and the memory of the affection of his sister in Scrooge’s psyche to lie dormant until the “first spirit” revives them.

Did Scrooge have an underlying obsessive-compulsive personality disorder? He certainly had a long-standing, fixed pattern of behavior that was outside the spectrum of “normal” and had negative consequences for him and others. These disorders are resistant to treatment and generally do not change easily, if at all.

One night Scrooge described hearing voices and seeing “ghosts.” The next day, unexpectedly, and without apparent cause, he suddenly began giving away substantial sums of money and exhibiting a markedly aberrant mood [friendly and exuberant]. His visual and auditory hallucinations might be diagnosed as a brief psychotic disorder and the question could be raised whether his behavior the next day was manic and today would be treated, perhaps with drugs.

Brief psychotic episodes [1 full day–1 month] may be spontaneous or precipitated by factors such as drugs, emotional trauma, etc. Bipolar disease may present with grandiose delusions, but there were no antecedent episodes. In some cultures and religions such behavioral episodes may be considered as “normal.” But Scrooge had no such affiliations. Some speculate that a brief psychotic episode can change one’s self-image, usually for the worse. Scrooge’s self-image, however, changed for the better. And the hallucinations were limited to only one night, thus not fitting the criteria for a brief psychotic episode.

Perhaps his hallucinations really were just vivid dreams. He recalled the visual and auditory sensations as if he had been awake. We all have had dreams like that. They seem very real, but they do not change our lives.

Charles Dickens, full-length portrait, seated at desk, facing left, in his study at Gad’s Hill Place. Created by Samuel Hollyer, circa 1875.
Tiny Tim and 19th-Century London

The major illness in *A Christmas Carol*, however, is the crippling disease suffered by Tiny Tim, who needed a crutch and metal braces. Many orthopedic, infectious, neurologic, congenital and other conditions could be the culprit. Dickens’ books were illustrated, but no visual clue about Tiny Tim is available, as he was not pictured in illustrations during Dickens’ lifetime.

We know that Tiny Tim survives after the latest and best treatment is financed by Scrooge after his “transformation” [from whatever cause]. So the disease must be amenable to treatment available in 1843.

One proposed theory suggests that type 1 renal tubular acidosis (RTN) might be the culprit. Treatment for symptoms such as weakness and failure to thrive [after all, he was called Tiny Tim] might have included rest, nutrition, trips to the country to rest, etc. Cod and halibut liver oil were common remedies for various afflictions. Dickens himself describes taking cod liver oil. Various “tonics” and mineral waters generally were advised. Some of these contained bicarbonate that might have served to ameliorate the acidosis. Scrofula (TB) and rickets were treated with “a prudent dose of alkaline carbonates.” If Tiny Tim received this treatment, his metabolic acidosis might have improved and also the osteomalacia and propensity for fractures. Of course if he received fish liver oil he would be getting Vitamin D as well.

The theory at that time was that disease transmission was due to “miasmas,” a mysterious property of the air. To protect them, children were kept fully clothed, including their arms and legs, and kept indoors, a certain impediment to achieving adequate Vitamin D levels.

At that time London industry was fueled by coal and the pollution was profound. The sky was “blackened with soot and particles.” And there were high concentrations of sulfur dioxide which block UV light.

The diet of Londoners, especially the poor, was mostly carbohydrates and deficient in Vitamin D. Commercial bread from small bakeries was adulterated with alum and aluminum salts, that precipitate phosphates leading to hypophosphatemia, which worsened the rickets. This was illegal. The inspectors, however, concentrated on large flour wholesalers so that flour for home-baking was not adulterated. Did Tiny Tim eat commercial or home baked bread?

We know that Mrs. Cratchit, Tiny Tim’s mother, cooked “pudding” but there is no mention of her baking bread. In 1857, John Snow first suggested the association of adulterated bread with rickets. The diet and lack of sunlight combined to produce profound Vitamin D deficiency and rickets.

It is estimated that 60% of children in London at that time had rickets. The first evidence that lack of an essential nutrient was the cause of rickets was noted in 1899. After multiple litters of lion cubs died of rickets at the London Zoo, survival was achieved with a diet that included cod liver oil. Subsequent investigations led to the discovery of Vitamin D and its structure, for which Adolph Windaus won the Nobel Prize in 1928.

Thus the improved nutrition, the Vitamin D in the cod liver oil and the exposure to sunlight at country sanatoria would have been appropriate treatment for Tiny Tim’s rickets.

Additionally, in Dickens’ era, fully 50% of London children had TB. The etiology of TB was unknown. Proof of its infectious etiology [Koch] appeared only in 1882.

If Tiny Tim had TB, why did it get better? Macrophages take up Vitamin D and this activates a series of intracellular processes resulting in the production of cathelicidin, a molecule that is bactericidal, especially to M tuberculosis. This also helps explain the success of treatment for TB with rest, adequate nutrition and sunlight in the pre-antibiotic era.

Type 1 RTN is a rare genetic disease. Rickets and TB were ubiquitous. Tiny Tim’s response to treatment and the prevalence of rickets and TB suggest that these were his afflictions.

All this clinical retrospection is interesting. But the power of this tale, as an allegory, is greater than its physiology. Perhaps the story of Scrooge’s “brief psychotic episode” or dreams [if you prefer], and Tiny Tim’s recovery, can “transform” the reader and lead to a better world. Thanks be to Charles Dickens.

Author

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Reconnecting with my Purpose in the Kingdom of Bhutan

ERIC COHEN, MD

[Editor’s note: To get to Bhutan, Dr. Cohen flew from Boston to Dubai to Bangkok and then took a flight to Paro, Bhutan on Druk Air. From Paro, it is an hour drive to the capital of Thimphu, Bhutan and the hospital where he worked. It takes about 24 hours of traveling to get there. Prior to departure, volunteers must have updated vaccinations for yellow fever and hepatitis.]

KEYWORDS: Heath Volunteers Oversees (HVO), international volunteer, medical mission, medical education, Bhutan

On March 11, 2016, I began my journey to the Kingdom of Bhutan, a small Buddhist country nestled in the Himalayas, on a volunteer medical mission through Heath Volunteers Oversees (HVO) with support from the Caroll M. Silver Traveling Fellowship. For me, volunteering abroad was more than just wanting to satisfy my need for an adventure or the need to conquer something new. If that were the case, I would have left on this mission at least five years earlier. Timing was critical to my plan; I finally had medical knowledge to share.

My mission to Bhutan was rooted in my need to show gratitude for all that has been given to me over the course of my medical school and residency career to date.

As a chief orthopaedic surgery resident at Rhode Island Hospital, I left Rhode Island with the intention of immersing myself in the Bhutanese culture with a goal of applying western medicine best practices to have an impact on the patient community served by the Jigme Dorji Wangchuck National Referral Hospital in Thimphu, Bhutan. But, I returned to the states five weeks later with a newfound connection to several core principles that will undoubtedly be invaluable to my future practice as an orthopaedic surgeon.

The first core principle I reconnected with was the importance of continuing medical education across all disciplines. To medical and surgical practitioners in the western world, this may seem obvious and easy to do. But, when you strip out luxuries like access to the latest literature, high-speed communication platforms and exposure to the most sophisticated experts in a given field, the value you place on medical education expands exponentially. Within my

Dr. Eric Cohen presenting Grand Rounds on pediatric septic arthritis of the hip to the Bhutanese orthopaedic surgeons, fellow (Heath Volunteers Oversees) HVO volunteers, fourth-year medical students, orthopaedic technicians and orthopaedic nurses.
first few days in Bhutan, I encountered a pediatric patient who came into the hospital from one of the smaller villages with an undiagnosed septic hip for two weeks. He presented with the classic signs of pediatric septic hip arthritis – high fevers, refusal to bear weight, and external rotation of the hip, however, he was referred for evaluation of shoulder and knee pain. I addressed this patient’s medical needs and also took the critical next step of hosting a Grand Rounds for an audience of attendings, nurses and orthopaedic technicians to educate them on this topic. Utilizing this pediatric patient as a classic case study, I am positive that future cases such as this will be diagnosed and treated in a timely manner.

This experience made me realize that while I now had the necessary technical skills, the most significant impact I could make over my five weeks was not through patient care – it was through education and mentorship. My Grand Rounds lecture as well as a dozen other seminars on the topics of midfoot and forefoot fractures, lower extremity casting and splinting, pediatric elbow fractures and general trauma and spine evaluation, circulated through the orthopaedic technicians to rural village clinics. I didn’t come back from Bhutan having treated every patient – I returned knowing I was able to share my knowledge with the staff so that they could help more patients by avoiding missteps in the future. I was touched to hear from one of my orthopaedic technicians recently, now a valued friend, that the orthopaedic team is continuing to apply some of the educational content and knowledge-sharing techniques I left them with a few months ago, like implementing daily review of all new consults and admissions and preoperative planning discussions.

Another key principle that emerged during my trip was approaching patient care with an appreciation and respect for the patient’s environment, culture and values. It would have been easy for me to approach each patient with the authoritative “surgeon-knows-best” persona that comes all too naturally for those of us in the field. But, that persona is lost on the 80-year-old Buddhist monk who just walked 20 miles from a rural village while clutching his prayer beads with a chronic infected lateral malleolar bursitis – a condition he developed due to prolonged meditation in the cross-legged position. Advising a monk to undergo a surgery that will take him away from his monastery for several weeks is not a conversation that has much room for the surgical super ego. Instead, I learned to approach this consult and others with a different style altogether. By mirroring the bedside manner of my attendings, one a Bhutanese native, and the other
COMMENTARY

two seasoned HVO volunteers, I began
to relax my body language, slow down
the cadence of my speech and demon-
strate active listening through playback
techniques. I was surprised how quickly
I settled into this new style and saw the
positive impact it had on my patients
and their families almost immediately.

Finding creative and sustainable
solutions was a final theme threaded
throughout my trip. Orthopaedic inju-
ries are the same in any country, but
their presentations and how you treat
them can be different and are contin-
gent on environmental circumstances. I
worked at the main referral hospital for
the entire country and the infrastructure
getting to this hospital was very poor,
which meant we were often seeing open
fractures that were several days old,
increasing the risk of infection. While
the injuries were the same as those I
dealt with domestically, my approach
to treatment was limited. I learned
to operate with limited fluoroscopy,
which increased my appreciation for
this technology.

I have been back in the United States
for several months and returned to a
fast-paced orthopaedic trauma fellow-
ship. But, amidst the fast-paced speed
of play in a level-one trauma hospital in a
country with seemingly infinite access
and resources, Bhutan is imprinted
in my memory and is an experience I
reflect on frequently. This experience
has truly enhanced my five years of
orthopaedic surgery residency training
and was essential to my development as
a caring, thoughtful physician. Recon-
necting with one’s purpose through
volunteerism can be a profound expe-
rience. The purpose of HVO is medical
education of physicians and ancillary
staff in developing nations to enact
long-term change and improvement in
patient care. Ironically, I think I learned
more from my patients and fellow Bhu-
tanese orthopaedic surgeons than they
did from me.

For fellow residents and professionals
considering volunteering abroad, HVO
is an invaluable resource with volunteer
opportunities throughout the world. For
more information regarding interna-
tional volunteer projects, visit the HVO
website at www.hvousa.org.

Acknowledgments
I am truly thankful for the Brown Orthopae-
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the Brown Orthopaedic Surgery Residency
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The Taktsang Palphug
Monastery, also known
as the Tiger’s nest, is a
sacred Buddhist temple
located on the side of
a cliff in Paro, Bhutan.
In the eighth century,
Guru Rinpoche, who is
credited with bringing
Buddhism to Bhutan, is
said to have flown from
Tibet on a flying tigress
and stayed and meditat-
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Wherever your travels take you, be sure to check the latest edition of RIMJ on your mobile device and send us a photo: mkorr@rimed.org.
Newer Treatment Strategies for Autoimmune Diseases

EDWARD V. LALLY, MD
GUEST EDITOR

In contemporary parlance, autoimmune disease has been used as a designation for a variety of chronic inflammatory disorders that are characterized by the presence of autoantibodies. This rubric has been applied to diseases whose etiologies are not infectious, neoplastic or degenerative in nature. The autoantibody profile may simply include a positive antinuclear antibody (ANA) test or it may be further defined by autoantibodies with specific identifiable autoantigens. By this description, autoimmune disease encompasses a wide variety of disorders manifesting as chronic inflammation confined to a tissue or organ or as a systemic inflammatory disease. Although, this nosology may serve to define syndromes that may be amenable to specific anti-inflammatory or immunosuppressive treatments, it has not served to advance our understanding of the etiology of these diseases, nor does it imply that the autoantibodies themselves directly participate in the pathogenesis of the disease. While these diseases may be “immunologically-mediated”, there is often very little evidence that these autoantibodies actually are involved in the disease pathogenesis.

A stricter definition of autoimmune disease would include the stipulation, that not only should autoantibodies be present, but that there is evidence to support the notion that they actually participate in the etiopathogenesis of the disorder. This definition adds a more rational framework for understanding autoimmune disease. It also allows for a better characterizing of the immunopathogenesis of these syndromes and can more readily allow for immunotherapy directed at specific pathways (“targeted therapies”).

In this issue of the Rhode Island Medical Journal, we review four inflammatory syndromes traditionally considered to be autoimmune in nature. By the above definition, two of these (SLE, pemphigus) would be viewed as autoantibody-mediated but the other two (cytopenias, CIDP) both likely fit the criteria even though the demonstration of specific autoantibodies in these disorders has been elusive. Other immunologically-mediated diseases (rheumatoid arthritis, multiple sclerosis, inflammatory bowel disease, myasthenia gravis, and autoimmune thyroid and liver disease) should also be viewed as autoimmune in nature. There have been significant developments in immunomodulatory therapy as reviewed in the introductory article by Lefebvre and McAuliffe. There is convincing evidence that the diseases listed in this review article are characterized by antigen-driven T-Cell activation and subsequent pro-inflammatory cytokine generation. However, effective strategies to abrogate T-cell activation and block resultant cytokines or cytokine receptors have outpaced the ability to identify specific triggering antigens or subsequent autoantibodies that are pathogenic. Nonetheless, the advent of such sophisticated targeted therapies will undoubtedly improve management and outcomes for immunologically-mediated diseases, some, but not all, of which should be considered auto-immune in nature.

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Targeted Immunomodulatory Therapy: An Overview
ASHLEY L. LEFEBVRE, PharmD, CDE; LAURA MCAULIFFE, PharmD

ABSTRACT
Monoclonal antibodies and other biologic response modifiers have allowed for targeted drug therapy in managing various autoimmune diseases. A number of immune pathways have been exploited in the development of targeted immunomodulatory therapies, including cytokine-directed therapies such as tumor necrosis factor-alpha and interleukins, integrins, B-cells, and co-stimulation modulators. With new targeted therapies in the pipeline, more options are becoming available for treatment of autoimmune diseases.

KEYWORDS: monoclonal antibodies, biologic response modifiers, immunomodulatory therapy

INTRODUCTION
With major advances in genetic sequencing and biomedical research, targeted therapy with monoclonal antibodies (mABs) has emerged as a successful strategy for managing autoimmune diseases. Treatment with mABs has the advantage of modifying specific immune pathways as opposed to other non-specific therapies. The first mAB (muromonab CD3) was developed from mice and approved in 1986 to prevent rejection of a kidney transplant. However, this first generation of mABs was not well-tolerated due to foreign recognition of the murine components by the patient’s immune system.

Since then, different approaches to producing chimeric [part mouse, part human] and fully humanized mABs have been discovered, rendering mABs less immunogenic. One such approach to producing mABs is from hybridomas, formed from the fusion of B-lymphocytes and immortal myeloma cells. The B-lymphocytes are obtained from the spleens of mice after they have been immunized against a specific antigenic determinant, or epitope. The hybridomas are cultured, leading to the generation of polyclonal antibodies. The polyclonal culture is screened for the desired antibody activity and then cloned.

The World Health Organization has policies for nomenclature of mABs. The structure is composed of four parts: the prefix, substem-A, substem-B, and suffix. Substem-A indicates the nature of the target of the mAB, such as tumor or cardiovascular. Substem-B indicates the originating species of the mAB [i.e. human, mouse, chimeric, etc.]. The suffix “-mab” is common to most mABs.

CYTOKINE-DIRECTED THERAPIES

TNFα Inhibitors
Tumor necrosis factor-alpha (TNFα) is a cell-signaling protein, or cytokine, that induces cell proliferation and differentiation through its interaction with TNF receptors on cell surfaces. TNFα plays a role early in many inflammatory immune processes. It is produced primarily by macrophages, but also by monocytes, B-cells, and other tissues. Activation of TNFα also leads to the secretion of interleukin (IL)-1 and IL-6, both proinflammatory cytokines. Dysregulation of TNFα can lead to the development of various autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD), ankylosing spondilitis, and psoriasis.

For instance, in IBD, TNFα secretion leads to the stimulation of endothelial cells to express adhesion molecules, facilitating migration of various white blood cells into inflamed tissue. TNFα inhibitor therapies are recombinant IgG mABs that essentially serve as decoy TNF receptors. They bind to TNFα molecules and prevent their interaction with TNF receptors, ultimately leading to suppression of the immune system and inflammatory responses. Examples of TNFα inhibitors are adalimumab and etanercept, with the latter possessing a longer half-life due to its dimeric nature. The goal of treatment with TNFα inhibitor therapy is to reduce inflammation and severity of symptoms, with the hope of achieving improved quality of life.

Interleukins
Interleukins are a large class of cytokines responsible for various immune responses, including inflammatory response mediation, lymphocyte growth and differentiation, and immune cell chemotaxis, which can be implicated in autoimmune diseases. Interleukin-17A (IL-17A), produced largely by T-helper 17 cells (Th17), acts directly on keratinocytes to stimulate various pro-inflammatory processes in plaque psoriasis. Interleukin-12 (IL-12) and interleukin-23 (IL-23) have been implicated in the production and development of Th17 cells, leading to psoriatic plaques and joint inflammation in psoriatic arthritis. In RA, IL-6 is released directly by synovial cells and macrophages into the synovium causing inflammation and destruction.
Monoclonal antibodies targeting interleukins are directed at cytokines involved in the production of interleukin, the interleukin itself, or receptors at which interleukin exerts its effect. Ustekinumab was developed against the p40 subunit of both IL-12 and -23, both important in differentiation of naïve T-cells to Th17 cells that produce IL-17A. Ustekinumab binds the p40 subunit of IL-12 and -23, resulting in reduced levels of Th17 cells. Secukinumab, an anti-IL-17A mAB, has been approved for treatment of plaque psoriasis. Inhibition of IL-17A prevents triggering of signaling and recruitment of numerous innate immune cells such as mast cells, neutrophils, and macrophages to psoriatic plaques. Tocilizumab, an anti-IL-6 receptor (IL-6r) recombinant mAB, blocks IL-6 signal transduction by binding to IL-6R embedded in the cell membrane and floating in soluble form in the blood. It also can dissociate already formed IL-6/IL-6R complexes, thereby effectively halting downstream signal transduction pathways that lead to joint inflammation and destruction in RA.

**SELECTIVE ADHESION MOLECULE INHIBITORS/ INTEGRIN RECEPTOR ANTAGONISTS**

Integrin molecules are conducive to lymphocyte trafficking by facilitating adhesion and migration from the vasculature into inflamed tissue. Integrin molecules are expressed on the surface of activated lymphocytes. Integrins interact with their receptors, which are the cell-adhesion molecules (CAMs) present on vascular endothelium. This interaction enables lymphocytes to migrate across the endothelium into tissues such as the brain and gut. Integrins α4β1 and α4β7 are implicated in multiple sclerosis and IBD, respectively.

Integrin receptor antagonist therapies are mABs that serve as decoys for the CAM receptors. They bind to integrin molecules to prevent interaction with CAMs, ultimately blocking migration of the activated T-lymphocytes into inflamed tissues. Selectivity of adhesion-molecule inhibitors can vary; for instance, natalizumab modulates lymphocyte trafficking in both the central nervous system and gut, while vedolizumab is specific to the gut. Increased specificity is advantageous for targeting desired tissues and limiting adverse effects, such as progressive multifocal leukoencephalopathy, which is a Black Box Warning for natalizumab. The currently available integrin receptor antagonist therapies are humanized mABs. Overall, the goal of integrin receptor antagonist therapy is to reduce migration of activated T-cells and limit progression of chronic inflammation.

**B-CELL DEPLETING THERAPIES**

B-cells play an important role in numerous autoimmune diseases. In healthy individuals, auto-reactive B-cells are removed from both the bone marrow and peripheral circulation prior to causing significant harm. In autoimmune diseases, a defect causes these auto-reactive B-cells to escape notice and produce antibodies, present “self” antigens, and produce various cytokines implicated in the disease process.

Monoclonal antibodies directed at B-cells are generally focused at B-cell depletion. The primary agent used for B-cell depletion in autoimmune diseases is rituximab, a mAB directed against the CD-20 antigen on B-lymphocytes. CD-20 is present on more than 95% of B-cells and plays a part in B-cell activation and cell-cycle progression. When rituximab binds to CD-20, it activates complement-dependent and antibody-dependent B-cell cytotoxicity, and B-cell apoptosis.

**OTHER BIOLOGIC RESPONSE MODIFIERS (BRMs)**

**Co-stimulation Modulators**

T-cells require two signals from antigen-presenting cells (APCs) to undergo activation: antigen presentation by histocompatibility molecules and a co-stimulatory signal provided by molecules on the APCs. In the CD80/86-CD28 co-stimulatory pathway, CD80 or CD86 on APCs binds with CD28 on the surface of T-cells and causes T-cell activation, proliferation, and cytokine production. Co-stimulatory pathways may also be inhibitory, as seen with cytotoxic T-lymphocyte antigen-4 (CTLA-4). CTLA-4 binds to CD80 or CD86, resulting in inhibition of T-cell responses by preventing release of interleukins and blocking cell-cycle progression. This pathway is important in the pathogenesis of RA, where activated T-cells are present in inflamed synovium.

Co-stimulation modulator antibodies target the signals required for co-stimulation of the T-cells to occur. Abatacept, a fusion protein used in the treatment of RA, consists of the extracellular domain of human CTLA-4 protein and the modified Fc region of human IgG1. The CTLA-4 portion of abatacept binds CD80/86 on APCs, thereby blocking the interaction between CD28 and APCs required for T-cell activation. The result of this blockade is a long-lasting attenuation of T-cell response. Belimumab, a human IgG1κ recombinant mAB used in the treatment of systemic lupus erythematosus, targets B-lymphocyte stimulator (BlyS), the co-stimulator for B-cell survival and function. BlyS binds to BlyS receptors and promotes the survival of autoantibody-producing B-cells by preventing their selection and apoptosis. Belimumab binds to soluble BlyS, preventing interaction with BlyS receptors and thereby decreasing B-cell survival and production of autoantibodies.

**Interleukin BRMs**

IL-1 is a system consisting of two pro-inflammatory ligands and the naturally occurring antagonist IL-1Ra. In RA, levels of IL-1 are elevated in plasma and synovial fluid. Anakinra, a recombinant human IL-1Ra, binds to IL-1 receptors to prevent intracellular signaling leading to cell activation and biological responses.
**Table 1. Currently Approved Monoclonal Antibodies and Biologic Response Modifiers**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Class</th>
<th>Clinical Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>Humira®</td>
<td>TNF inhibitor</td>
<td>Rheumatoid arthritis, Psoriatic arthritis, Plaque psoriasis, Crohn’s disease, Ulcerative colitis, Ankylosing spondylitis, Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Enbrel®</td>
<td>IL-1 blocker</td>
<td>Rheumatoid arthritis, Psoriatic arthritis, Plaque psoriasis</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
<td>Cimzia®</td>
<td>IL-12 and IL-23 inhibitor</td>
<td>Psoriatic arthritis, Plaque psoriasis</td>
</tr>
<tr>
<td>Golimumab</td>
<td>Simponi®</td>
<td>IL-17A receptor antagonist</td>
<td>Plaque psoriasis, Ankylosing spondylitis, Psoriatic arthritis</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Remicade®</td>
<td>IL-17A receptor antagonist</td>
<td>Plaque psoriasis, Ankylosing spondylitis, Psoriatic arthritis</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Kineret®</td>
<td>IL-1 antagonist</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Canakinumab</td>
<td>Ilaris®</td>
<td>IL-1 antagonist</td>
<td>Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>Actemra®</td>
<td>IL-6 antagonist</td>
<td>Rheumatoid arthritis, Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>Stelara®</td>
<td>IL-12 and IL-23 inhibitor</td>
<td>Psoriatic arthritis, Plaque psoriasis</td>
</tr>
<tr>
<td>Secukinumab</td>
<td>Cosentyx®</td>
<td>IL-17A receptor antagonist</td>
<td>Psoriatic arthritis, Ankylosing spondylitis, Psoriatic arthritis</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>Taltz®</td>
<td>IL-17A receptor antagonist</td>
<td>Psoriatic arthritis, Ankylosing spondylitis, Psoriatic arthritis</td>
</tr>
<tr>
<td>Abatcept</td>
<td>Ocrevus®</td>
<td>Co-stimulation blocker of CD-28</td>
<td>Rheumatoid arthritis, Juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Belimumab</td>
<td>Benlysta®</td>
<td>BLyS inhibitor</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Vedolizumab</td>
<td>Entyvio®</td>
<td>Integrin receptor antagonist</td>
<td>Crohn’s disease, Ulcerative colitis</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Tysabri®</td>
<td>Anti-integrin antibody</td>
<td>Crohn’s disease, Ulcerative colitis, Multiple sclerosis</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Rituxan®</td>
<td>Anti-CD20 antibody</td>
<td>Rheumatoid arthritis, Lupus nephritis, Idiopathic thrombocytopenic purpura, Graft-versus-host disease</td>
</tr>
</tbody>
</table>

**Table 2. Monoclonal Antibodies and Biologic Response Modifiers in the Pipeline**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Stage in Development</th>
<th>Trial Names</th>
<th>Class</th>
<th>Clinical Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brodalumab</td>
<td>Phase III clinical trials</td>
<td>AMAGiNE and AMViSioN</td>
<td>IL-17A receptor monoclonal antibody</td>
<td>Plaque psoriasis, Psoriatic arthritis, Ankylosing spondylitis</td>
</tr>
<tr>
<td>Guselkumab</td>
<td>Phase II clinical trials</td>
<td>X-PLorE</td>
<td>IL-23 monoclonal antibody</td>
<td>Plaque psoriasis</td>
</tr>
<tr>
<td>Tildrakizumab</td>
<td>Phase III clinical trials</td>
<td>-</td>
<td>IL-23 p19 subunit monoclonal antibody</td>
<td>Plaque psoriasis</td>
</tr>
<tr>
<td>Anifrolumab</td>
<td>Phase III clinical trials</td>
<td>-</td>
<td>IFN Type I receptor monoclonal antibody</td>
<td>Systemic lupus erythematosus</td>
</tr>
<tr>
<td>Ozoralizumab</td>
<td>Phase II clinical trials</td>
<td>-</td>
<td>Anti-TNFα Nanobody</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Etrolizumab</td>
<td>Phase III clinical trials</td>
<td>-</td>
<td>Integrin inhibitor</td>
<td>Crohn’s disease</td>
</tr>
</tbody>
</table>

**CONCLUSION**

Monoclonal antibodies and other BRMs have allowed for targeted drug therapy in managing various autoimmune diseases. A number of immune pathways have been exploited in the development of mAbs by targeting cytokines, cell-adhesion molecules, co-stimulation signals, and B-cells (Table 1). Promising new agents are in the pipeline (Table 2), providing additional options for managing autoimmune conditions.

**References**


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ABSTRACT
Systemic lupus erythematosus (SLE) is a chronic, complicated and challenging disease to diagnose and treat. The etiology of SLE is unknown, but certain risk factors have been identified that lead to immune system dysfunction with antibody formation and immune complex deposition. This immune system dysregulation causes organ injury, contributing to the variable manifestations and relapsing-remitting course of the disease. Criteria were created to aide in the diagnosis, focusing on clinical manifestations and antibody profiles specific to SLE. Treatment options are limited to a few medications to control the inflammation and decrease organ damage. Continuing investigations into the pathogenesis of SLE has led to new discoveries, making more medications available to treat this difficult disease.

KEYWORDS: systemic lupus erythematosus, antibodies, autoimmunity, treat to target, B-cell depletion and modulation, interferon blocking agents

SLE EPIDEMIOLOGY
SLE is seen worldwide, with incidence and prevalence rates differing geographically. Studies have shown that the incidence rate of SLE around the world is about 1 to 10 per 100,000 person-years, while the prevalence rates range from 20–70 per 100,000 person-years. In the United States (US), the all race incidence was found to be 5.1 per 100,000 person-years and the prevalence was estimated to be over 300,000 persons. SLE predominantly affects women, with a reported peak female-to-male ratio of 12:1 during the childbearing years. The disease can also be seen in children and the elderly with a narrower gender distribution. Studies have shown racial/ethnic variations, with SLE being more common in non-Caucasian persons, occurring three to four times more often in African-Americans. In addition to African-Americans, Hispanics and Asians develop SLE more frequently than Caucasians. In these populations, SLE tends to be more active and severe, with a higher risk of relapses and organ system involvement or damage. Even with advances in diagnosis and treatment of the disease, the mortality risk in patients with SLE is higher than that of the general population. For newly diagnosed patients, the 5-year survival rate is over 90% and the 15 to 20 year survival rate is about 80%. Worse outcomes and higher mortality risk correlated with this ethnic disparity, which may be influenced by a lower socioeconomic status as well.

SLE PATHOGENESIS
The etiology of SLE is unknown. Certain risk factors have been identified and shown to contribute to disease susceptibility or activate the immune system causing an inflammatory response, ultimately leading to the development of the disease. Predisposition to SLE is influenced by genetic factors. The female predominance in SLE, may be explained, in part, by the contribution of certain hormones. Environmental factors, such as smoking, exposure to ultraviolet light, viral infections, and specific medications (e.g. sulfonamide antibiotics) are known to trigger SLE. The pathogenesis of SLE is complex with contribution from many components of the immune system. With the underlying genetic predisposition and in response to various triggers, the balance of the immune system shifts towards reacting against itself, rather than self-tolerance. T and B cells become activated, leading to antibody production and eventual immune complex formation. These complexes circulate and deposit in critical tissues causing organ injury.

SLE DIAGNOSIS
Classification criteria have been derived for SLE, mainly for research purposes, to achieve population homogeneity among research studies. The American College of Rheumatology (ACR) published criteria in 1982, which were revised in 1997 (Table 1). The Systemic Lupus Collaborating Clinics (SLICC) international group undertook the evaluation and further revision of the above criteria resulting in a new classification system that is based on clinical and immunologic manifestations (Table 1). In an actual clinical practice setting, both criteria were analyzed, it was determined that the SLICC 2012 criteria were more sensitive and may allow patients to be classified with SLE earlier in the disease course. In the clinical setting, these criteria can be used as an aid in diagnosis, but formal diagnostic criteria for SLE are lacking.
Table 1. Classification Criteria for Systemic Lupus Erythematosus

<table>
<thead>
<tr>
<th>Category</th>
<th>Criteria</th>
<th>ACR 1997</th>
<th>SLICC 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1. Malar Rash</td>
<td>1. Acute cutaneous lupus (including malar rash, photosensitive lupus rash) OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Discoid Rash</td>
<td>Subacute cutaneous lupus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Photosensitivity</td>
<td>2. Chronic cutaneous lupus (including discoid rash)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. Oral or Nasopharyngeal ulceration</td>
<td>3. Oral or nasal ulcers</td>
<td>4. Nonscarring alopecia</td>
</tr>
<tr>
<td>Joints</td>
<td>5. Nonerosive arthritis involving ≥ 2 peripheral joints characterized by pain, swelling or effusion</td>
<td>5. Synovitis involving ≥ 2 peripheral joints characterized by swelling or effusion or tenderness and ≥ 30 minutes of morning stiffness</td>
<td></td>
</tr>
<tr>
<td>Serositis</td>
<td>6A. Pleuritis (pleuritic pain/rub or pleural effusion) OR</td>
<td>6. Serositis (any of the following)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6B. Pericarditis (by EKG, rub, or pericardial effusion)</td>
<td>- pleurisy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- pleural effusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- pleural rub</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- pericardial pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- pericardial effusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- pericarditis by EKG</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>7A. Persistent proteinuria (&gt; 0.5g/day or &gt; 3+ dipstick) OR</td>
<td>7. Renal (any of the following)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7B. Cellular casts</td>
<td>- urine protein/creatinine (24 hour urine protein) &gt; 0.5g/24hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- red blood cell casts</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>8A. Seizures</td>
<td>8. Neurologic (any of the following)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8B. Psychosis</td>
<td>- seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- psychosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- mononeuritis multiplex</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- myelitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- peripheral or cranial neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- acute confusional state</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>9A. Hemolytic anemia</td>
<td>9. Hemolytic anemia</td>
<td>10. Leukopenia (&lt;4,000/mm3 at least once) OR</td>
</tr>
<tr>
<td></td>
<td>9B. Leukopenia (&lt;4,000/mm3 on ≥ 2 occasions) OR</td>
<td>9. Hemolytic anemia</td>
<td>Or Lymphopenia (&lt;1,000/mm3 at least once)</td>
</tr>
<tr>
<td></td>
<td>9C. Lymphopenia (&lt;1,500/mm3 on ≥ 2 occasions) OR</td>
<td>9. Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9D. Thrombocytopenia (&lt;100,000/mm3)</td>
<td>9. Hemolytic anemia</td>
<td></td>
</tr>
<tr>
<td>Immunologic</td>
<td>10A. Anti-dsDNA</td>
<td>1. Antinuclear antibody</td>
<td>1. Antinuclear antibody</td>
</tr>
<tr>
<td></td>
<td>10B. Anti-Sm</td>
<td>2. Anti-dsDNA</td>
<td>2. Anti-dsDNA</td>
</tr>
<tr>
<td></td>
<td>10C. Antiphospholipid Antibody (any of the following)</td>
<td>3. Anti-Sm</td>
<td>3. Anti-Sm</td>
</tr>
<tr>
<td></td>
<td>- anticardiolipin antibodies (IgG or IgM)</td>
<td>4. Antiphospholipid antibody (any of the following)</td>
<td>4. Antiphospholipid antibody (any of the following)</td>
</tr>
<tr>
<td></td>
<td>- lupus anticoagulant</td>
<td>- lupus anticoagulant</td>
<td>- lupus anticoagulant</td>
</tr>
<tr>
<td></td>
<td>- false-positive RPR</td>
<td>- false-positive RPR</td>
<td>- medium or high titer anticardiolipin (IgA, IgG, or IgM)</td>
</tr>
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<td></td>
<td>- false positive syphilis test or &gt; 6 months (confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test)</td>
<td>- anti-β2 glycoprotein I (IgA, IgG, or IgM)</td>
<td>- anti-β2 glycoprotein I (IgA, IgG, or IgM)</td>
</tr>
<tr>
<td></td>
<td>11. Positive antinuclear antibody</td>
<td>5. Low complement</td>
<td>5. Low complement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- low C3, C4, CH50</td>
<td>6. Direct Coombs test</td>
</tr>
<tr>
<td>Classification of SLE</td>
<td>- Satisfy four out of the 11 criteria</td>
<td>6. Direct Coombs test</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Satisfy four of the criteria, including one clinical criterion and one immunologic criterion OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>- biopsy-proven nephritis compatible with SLE and with ANA or anti-dsDNA antibodies</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SLICC = Systemic Lupus International Collaborating Clinics; ACR = American College of Rheumatology; SLE = systemic lupus erythematosus; Anti-dsDNA = anti-double-stranded DNA; Anti-Sm = anti-smith antibody; EKG = electrocardiogram; RPR = rapid plasma regain; CH50 = 50% hemolyzing dose of complement
SLE CLINICAL AND LABORATORY MANIFESTATIONS

SLE has a variable, relapsing-remitting course and clinical symptoms vary between patients, depending on which organ systems are affected. The above criteria incorporate the major and common organ systems that can be affected in SLE including skin, mucus membranes, joints, kidneys, brain, lungs, heart and hematologic system (Table 1). Clinical and laboratory surveillance is also important to assess and monitor for the development of any new symptoms or findings. A serious manifestation of SLE, with resultant increased morbidity and mortality, is lupus nephritis (LN). Treatment is based on the findings on a kidney biopsy. Neuropsychiatric involvement is rare but difficult to diagnose. It may not correspond to overall SLE activity. SLE patients may also have comorbidities, further complicating their disease.

Atherosclerosis is common, presenting as coronary artery disease (CAD), or cerebral or peripheral vascular diseases. CAD is linked to increased morbidity and mortality, with SLE women aged 35-44 years old being more than 50 times more likely to have a myocardial infarction than women of a similar age without SLE. Even though traditional cardiovascular risk factors do not fully explain the accelerated rate of atherosclerosis in SLE patients, they should be addressed routinely and modified to prevent further morbidity or mortality.

Autoantibody production is fundamental to the pathogenesis of SLE. These autoantibodies are directed against nuclear or cytoplasmic antigens and are known as antinuclear antibodies (ANA). ANAs are included in the diagnostic criteria (Table 1) and are seen in more than 95% of SLE patients. Other antibodies have been identified that are recognized based on their targeted autoantigens and are collectively known as anti-extractable nuclear antigens (ENA). Anti-double stranded DNA antibody (anti-dsDNA) is highly specific (95% specific) for SLE, especially with renal disease. Anti-Sm antibodies (antibodies against Sm core particles) are unique and highly specific for SLE with renal disease, although seen in only about 20-30% of SLE patients overall. Other antibodies may be seen in SLE, but are not specific for the disease and can be seen in other autoimmune conditions. For example, anti-ribonucleoprotein (anti-RNP) is seen in 30-40% of SLE patients, but is highly associated with mixed connective tissue disease. Anti-Ro (anti-SSA) and anti-La (anti-SSB) are seen in 40% of SLE patients, but have a stronger association with Sjogren’s syndrome. Anti-ENA antibodies are used as serologic markers for SLE. Anti-dsDNA antibodies and complement components (C3 and C4) may be used to monitor SLE activity, especially in the setting of lupus nephritis. Another set of antibodies seen in 30-40% of SLE patients are the antiphospholipid antibodies, which are lupus anticoagulant, anticardiolipin antibodies, and anti-β2-glycoprotein 1 antibodies. About 10-15% SLE patients can have antiphospholipid syndrome, manifested by recurrent venous or arterial thrombosis or pregnancy morbidity.

TREAT TO TARGET

Utilization of corticosteroids (CS) in SLE management began in the 1950s and was a major important therapeutic milestone. However, challenges in SLE treatment remain to this day. Retrospective studies have provided evidence that increased disease activity in rheumatologic or autoimmune disorders is related to future organ damage and death. In response to this finding, the “treat to target” strategy to achieve disease remission was established and attainable in rheumatoid arthritis. This concept is gaining momentum in the care of SLE patients with new treatment options available and/or emerging medications in the research pipeline. Currently there are only three agents, in addition to CS, that are FDA approved for SLE treatment. The challenge has been to create guidelines for the management and treatment of SLE due to the lack of quality evidence for almost all aspects of SLE, except lupus nephritis.

BASIC THERAPY

Management of SLE patients begins with basic recommendations including avoidance of sunlight and use of high-SPF sunscreen (> 35), with screening and counseling for modifiable cardiovascular risk factors such as cigarette smoking and uncontrolled HTN. Family planning discussions should be considered with SLE patients of reproductive age. Supplementation of calcium and vitamin D is recommended. The general approach to the use of pharmacological agents depends on specific organ involvement and is tailored to other SLE patient characteristics, such as ethnicity and comorbid conditions.

ANTIMALARIALS

Antimalarial medications, such as hydroxychloroquine (HCQ), have proved useful in treating milder manifestations of lupus including dermatitis, arthritis and constitutional symptoms. The exact mechanism of action of antimalarials is unknown. Support for the use of HCQ as background therapy in patients with SLE emerged after a pivotal Canadian study found that HCQ reduced flares in SLE patients compared to subjects in whom the medicine was withdrawn. Subsequent analysis linked HCQ to the reduction of organ damage, thrombosis and improvement in survival. HCQ has been shown to favorably modulate lipid profiles in patients receiving CS.

CORTICOSTEROID TREATMENT IN SLE

Considered the cornerstone of SLE treatment, CS have the major advantage of rapid control of SLE activity, from controlling skin or joint disease, to severe and life threatening complications such as vasculitis and nephritis. CS are often given orally, but for severe life-threatening complications, intravenous forms of CS are usually administered. Short
term use of CS may be necessary and often convenient to control SLE flares, but long-term use is related to significant side effects. Doses of prednisone greater than 10–19 mg a day increase the risk of cardiovascular events 2.4 times compared to daily doses below 9 mg. The risk of long term CS use on skeletal health is well established and will not be addressed here.

FROM OTCs TO CHEMOTHERAPY
In addition to antimalarials, non-steroidal anti-inflammatory drugs [NSAIDs] and traditional agents used for rheumatoid arthritis, such as methotrexate, have been used to control mild to severe arthralgias and arthritis. Immunosuppressive drugs such as azathioprine [AZA] in doses of 2-2.5mg/kg/d may be used as steroid sparing agents to treat the various manifestations of SLE. For the most life-threatening SLE organ manifestations such as neuropsychiatric, LN, pulmonary hemorrhage and systemic vasculitis, high-dose or pulse steroids as the initial treatment are being used, usually followed by high potency steroid sparing agents. Cyclophosphomide (CyC), an alkalizing agent, has emerged as the gold standard medication for the management of lupus nephritis after an NIH study which showed that SLE patients on CyC had better renal survival than patients on CS alone. The dose and regimen for CyC was standardized since the NIH experience, but based on the Euro-lupus trial, the lower dose of CyC can be safely used in selected populations, without compromising its efficacy. CYC is used as induction therapy to further decrease inflammation and decrease disease activity. Due to its significant toxicity, most SLE patients are managed with maintenance medications that include AZA or mycophenolate mofetil [MMF] to reduce the frequencies of flares. Nearly 25 years since the publication of the pivotal NIH study of the use of CYC for the management of LN, MMF proved to be non-inferior and for some populations, non-Caucasians, even superior to CYC as an agent for induction of remission of LN.

B-CELL DEPLETION OR MODULATION
B cells play a central role in the pathogenesis of active lupus through cytokine production, presentation of self antigens, activation of T cells and antibody production. Better understanding of B cell function in SLE pathology directed investigators to conduct trials of rituximab (RTX) for the treatment of severe SLE. RTX is a chimeric mouse/human monoclonal antibody (mAb) against the CD20 antigen on B cells, rapidly decreasing B cells, hence reducing inflammation. The important study of the utilization of RTX in lupus nephritis did not meet the primary end point of reduction in proteinuria; despite reducing the level of complements and dsDNA. Critics of the study point to possible faulty study design [small number of patients, use of high dose of steroids, short study time] as a reason for not reaching statistical significance. Further, the suboptimal response to RTX may be related to immune complex-mediated advanced kidney injury rather than antibody production related damage. Still, “off label” RTX is used as a second-line agent in lupus complications like neuropsychiatric SLE and vasculitis in addition to its proven efficacy in idiopathic thrombocytopenic purpura [ITP] and autoimmune hemolytic anemia [AHA]. The most common side effects of RTX are related to post infusion complete blood count [CBC] abnormalities. Epratuzumab is another B cell therapy targeting the CD22 molecule on B cells. CD22 is responsible for B cell activation and function. This anti-CD 22 agent, that modulates B cell response, has entered late phases of clinical trials with promising preliminary data. Epratuzumab was first studied in trials which ended prematurely due to shortage of the drug. Data analysis showed that epratuzumab may decrease disease activity in SLE, but the authors were unable to draw definitive conclusions. Another trial, studying the same molecule, showed improvement in most areas of SLE activity, from mucocutaneous to renal and neuropsychiatric manifestations. Headache and nausea were the most common side effects.

TARGETED THERAPIES
BLyS [a B lymphocyte stimulator] is responsible for B cell survival in some SLE patients and is targeted by belimumab, a new FDA-approved drug. This fully human mAb binds to BAFF [B-cell activating factor] receptor on mature B cells decreasing their activation, antibody secretion and possibly preventing T cell activation as well. Belimumab was found to be beneficial in patients with SLE-related dermatitis, mucositis and arthritis, but was not specifically studied in LN. In one clinical trial, a subgroup of patients with elevated dsDNA and low C3 and C4, benefited from this medication the most. Belimumab may constitute a viable, but expensive, option to treat SLE patients who are not responding or intolerant to first line therapies. It has an acceptable safety profile.

INTERFERON BLOCKING AGENTS
Interferon α [INF] has been linked to accelerated disease activity and is the main target of antimalarial therapy in SLE. INFα blocking therapies entered phase II clinical trials and show promising results in moderate to severe SLE. Preliminary data presented in abstract form in 2014 showed promising results with sifalimumab, mAb against INFα. This INF inhibitor reduced baseline moderate to severe SLE mucocutaneous involvement, as well as decreased arthritis and fatigue scores. It did not improve serological markers of active disease, such as dsDNA and complement levels. For this medication, the overall safety data was acceptable, with infections and headache as the most commonly reported adverse effects. Novel studies capitalize on INFγ with INFγ gene expression seen in peripheral blood of subjects with
autoimmune disorders, such as SLE. A recent randomized controlled trial of a mAb against INFγ (molecule AMG 811) used in subjects with mild to moderate SLE showed dose dependent modulation of INF gene expression and reduction of the inflammatory protein linked to the prediction of future flares and level of disease activity.25

CONCLUSION

SLE remains a challenging disorder that requires an interdisciplinary approach with a team of health-care providers to diagnose, manage and tailor treatment to individual patient needs. Continued dedication and research into the pathogenesis of SLE to identify specific immunologic targets for potential therapies, will bring more exciting new medications and hope to SLE patients to better control this difficult and unique disease.

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Pemphigus: Pathogenesis to Treatment
CHRISTOPHER DIMARCO, MD

ABSTRACT
Pemphigus vulgaris (PV), pemphigus foliaceus (PF), and paraneoplastic pemphigus (PNP) are a group of rare and fatal blistering diseases involving autoantibodies that target desmosomal proteins. The pathogenesis of pemphigus involves the production of activated B-cells and IgG with stimulation by IL-4 by T-helper 2 cells. Clinically these diseases present most often with epidermal erosions of the mucosae and skin caused by rapid rupturing of flaccid bullae. These lesions correlate histologically with splits forming in the epidermis, leaving a blister roof composed of a few cell layers. Standard treatment of pemphigus involves oral corticosteroids, often with the addition of adjuvant therapies, to improve disease control, minimize corticosteroids side-effects, and increase the odds of remission.

KEYWORDS: pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, desmoglein 1, desmoglein 3, corticosteroids

INTRODUCTION
Pemphigus includes a group of blistering diseases involving autoantibodies that target proteins found in the desmosome, intercellular adhesion protein complexes. Most forms of pemphigus are classified as being a subtype of pemphigus vulgaris (PV), pemphigus foliaceus (PF), or paraneoplastic pemphigus (PNP). They are a rare group of disorders that have an incidence of 2-10 cases per one million inhabitants in some areas of the world and a prevalence of 0.1-0.7 per one hundred thousand inhabitants.1,2 Pemphigus was a highly fatal disease until the introduction of corticosteroids (CS) which have reduced its mortality rate from 75% to less than 10%, with most morbidity and mortality today due to iatrogenic causes rather than the disease itself.3,4 The one exception is paraneoplastic pemphigus, which has a mortality rate around 50%, most often due to pneumonia, the associated malignancy, or pulmonary involvement, resulting in bronchiolitis obliterans, despite treatment.5

PATHOGENESIS
The pathogenesis underlying all forms of pemphigus involves the development of autoantibodies to the desmosomal proteins, which can be found in many areas of the body, but which play a major role in the epidermal layers of the integumentary system. PV and PF are caused primarily by antibodies to desmoglein 1 (Dsg 1) in PF, desmoglein 3 (Dsg 3) in mucosal dominant PV, or both in mucocutaneous PV.6 Dsg 1 and 3 are found in varying amounts in the epidermis of the skin and mucosa. Dsg 1 is found in higher amounts in the upper layers of the epidermis, especially on the skin, while Dsg 3 is found in the lower layers of the epidermis with higher concentrations in the mucosa and skin.6 It is this variability in distribution which explains the 3 distinct clinical diseases.

The disease usually occurs in patients with certain HLA genotypes who generate B-cells responsible for the specific autoantibodies. The activation of these B-cells requires a complex interaction with CD4+ T helper 2 (Th2) cells and it is this Th2 cell over-activation that leads to the autoantibody production that is necessary for PV and PF.1,2,6 Th2 cells are known for secreting multiple interleukins (IL), of which IL-4 plays a major role in pemphigus and the humoral immune response.2 IL-4 promotes antibody production by primed B cells and an isotype switching from IgG1 to IgG4 antibodies which have been shown to be important in the active form of PF and PV.2,6 IL-4 also perpetuates the disease by causing naïve CD4+ T cells to differentiate into Th2 cells.6 The production of autoantibodies and epitope binding is sufficient to cause loss of adhesions between desmosomes leading to separation of keratinocytes which is directly related to disease activity.1 Therefore the disease does not require other components of the immune system for activity, such as complement or cytotoxic T cells. Based on this pathogenesis, treatment for pemphigus focuses primarily on the prevention of antibody production and prevention of isotype switching from an IgG1 to IgG4. When pemphigus enters remission there is a known upregulation of IL-10 and a Th1 response that induces antibody isotype switching from IgG4 back to IgG1.1,2,6 Tumor necrosis factor α, IL-1, and other cytokines also play a smaller role in the pathogenesis of pemphigus.2

PNP is unique from PV and PF in that it may contain autoimmune antibodies to Desmoglein 1 and 3, but has more specific antibodies to envoplakin and perilplakin.7 While envoplakin and perilplakin are the most specific for PNP, patients with this disease can develop multiple autoantibodies primarily to desmosomal proteins, including the
plakin family of proteins [plectin, BP230, and desmoplakin], desmocollins, and alpha-2-macroglobulin-like antigen-1.5,8

CLINICAL

While pemphigus is classified as an auto-immune blistering disease, usually the most prominent findings are epidermal erosions from rapid rupturing of blisters with thin roofs. PV often begins with oral erosions primarily involving the buccal and gingival mucosa. If patients have developed antibodies to both Dsg 1 and 3, they will likely manifest erosions and flaccid bullae on the skin over weeks to months. Generally the chest, face, scalp, upper back, and areas of trauma are common sites for cutaneous involvement.1,6,9,10 PF often can present very similarly to the cutaneous involvement of PV. Clinical differences include the lack of mucosal involvement and an exfoliative presentation due to the shallow depth that the erosions occur in the epidermis.9 (Table 1)

PNP, due to the presence of multiple different autoantibodies, may have a more variable clinical presentation. All patients present with severe involvement of at least a single mucosal surface, with the majority reporting oral involvement. However, there is a high percentage of patients who have involvement of the ocular, genital, and nasal mucosa.5 Up to two thirds of patients will have cutaneous involvement presenting with classic erosions of pemphigus. But as many as 50% of patients will present with cutaneous lesions similar to erythema multiforme, bullous pemphigoid, and lichen planus. The most commonly reported malignancies with PNP are lymphoid malignancies, most often non- Hodgkin lymphoma and chronic lymphocytic leukemia, followed by Castleman disease, thymoma, and a mix of other solid organ tumors.5,7 Of note, only two thirds of patients will have been diagnosed with a malignancy when presenting with PNP.9

The diagnosis of any patient with a clinical suspicion for pemphigus is best confirmed with a combination of histopathology and laboratory testing. Most commonly a biopsy of a fresh vesicle or the edge of a blister, with adjacent non-blistered skin, should be performed for histopathology. A biopsy of normal skin at least 1cm away from any blistered or inflamed skin should also be obtained and sent for direct immunofluorescence (DIF).9 The key histological feature of pemphigus is an intra-epidermal split with the loss of adhesion and separation of normal appearing keratinocytes referred to as acantholysis. In PV, the histology shows suprabasilar split with acantholysis of keratinocytes and DIF will be positive for intercellular IgG involving the entire epidermis. PF will have a subcorneal split with acantholysis of keratinocytes and a DIF showing positive intercellular staining in the upper epidermal layers.9 PNP can have a histology and DIF with variable amounts of suprabasal acantholysis, lymphocytic infiltrate, and necrotic keratinocytes.7 (Table 1) Histopathology and DIF can have overlapping features between the various forms of pemphigus. But the histologic picture may be non-diagnostic and serologic studies are recommended. Enzyme-linked immunosorbent assay [ELISA] to quantitate Dsg antibody titers can be done or, if unavailable, serum should be sent for indirect immunofluorescence (IIF) on monkey esophagus for a qualitative measurement of serum Dsg antibodies.6-10 Specific to PV, ELISA can be used to monitor Dsg 3 antibodies which can correlate with disease severity.10 Specific to PNP, if suspected, IIF can be performed on monkey or rat bladder urothelium which lacks Dsg 1 and 3 but still contains plakins making it a specific test for PNP.5,8

TREATMENT

Due in part to its rarity and the lack of standard definitions for tracking disease activity, studies on the treatment of pemphigus are few and limited by small sample sizes.3 First-line

Table 1. Summary of disease classification, clinical features, autoantibody targets, histological, and immunofluorescence findings.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Clinical Features</th>
<th>Autoantibodies</th>
<th>Histology</th>
<th>Direct Immunofluorescence</th>
<th>Indirect Immunofluorescence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus Vulgaris – Mucosal Dominant</td>
<td>Mucosal erosions and flaccid bullae</td>
<td>Desmoglein 3</td>
<td>Suprabasilar split with acantholysis</td>
<td>Intercellular IgG on the entire epidermis</td>
<td>Intercellular IgG on Monkey Esophagus</td>
</tr>
<tr>
<td>Pemphigus Vulgaris – Mucocutaneous</td>
<td>Cutaneous and mucosal erosions and flaccid bullae</td>
<td>Desmoglein 1 and 3</td>
<td>Suprabasilar split with acantholysis</td>
<td>Intercellular IgG on the entire epidermis</td>
<td>Intercellular IgG on Monkey Esophagus</td>
</tr>
<tr>
<td>Pemphigus Foliaceus</td>
<td>Cutaneous erosions and exfoliative dermatitis</td>
<td>Desmoglein 1</td>
<td>Subcorneal split with acantholysis</td>
<td>Intercellular IgG on the upper epidermis</td>
<td>Intercellular IgG on Monkey Esophagus</td>
</tr>
<tr>
<td>Paraneoplastic Pemphigus</td>
<td>Severe mucosal involvement, pemphigus-like, erythema multiform-like, or lichen planus-like cutaneous lesions</td>
<td>Envolaplakin, Periplakin, Plectin, BP230 Desmoplakin, Desmocollin, Desmoglein 1 and 3, Alpha-2-macroglobulin-like antigen-1</td>
<td>Suprabasilar split with acantholysis, lymphocytic infiltrate, and necrotic keratinocytes</td>
<td>Intercellular IgG on the entire epidermis</td>
<td>Intercellular IgG on Monkey Esophagus, Rat Bladder, and Monkey Bladder</td>
</tr>
</tbody>
</table>
therapy for all forms of pemphigus should be CS. Initial daily doses equivalent to 0.5 to 1.0 mg/kg of prednisone are recommended. However, smaller studies have shown that there may be no difference in outcomes for either initial dose. IV methylprednisolone has been shown in pemphigus patients to decrease tumor necrosis factor α and interleukin 6.2

With the initiation of a CS it is common practice to also start an adjuvant therapy for disease control. The exact mechanism of immunosuppressive medications in pemphigus is unknown but it is believed that these therapies act by inhibiting B cell and autoantibody production which contribute to disease activity.2 Adding an adjuvant agent is proven to lower the risk of relapse. However this effect is lost when comparing specific adjuvant medications. Also, adjuvant therapy does not improve remission rates, time to disease control, time to relapse, or the incidence of death in pemphigus.3,4

In addition to traditional immunosuppressive medications, another recently utilized adjuvant is intravenous immunoglobulin (IVIG). IVIG has been shown to decrease IL-1 levels in patients with PV and also provide immune modulation and reconstitution.2 IVIG also causes a decrease in IgG4 and IgG1 antibodies to Dsg 1 and 3 within 2 weeks of therapy.11 A recent meta-analysis demonstrated that IVIG was the only adjuvant that improved disease control compared to more traditional immunosuppressive medications.4 In combination with CS, IVIG has been shown to induce clinical improvement in over half of treated patients.11

B-cell depleting therapies have also been studied as standard adjuvant therapy for the treatment of pemphigus and have increased remission rates up to 65%.10 Rituximab is a monoclonal antibody against the CD20 surface glycoprotein on mature B cells while sparing plasma cells. In pemphigus there is a decrease in autoantibodies to Dsg and peripheral blood B cells that lasts several months. Those levels may rise with the return of peripheral B cells and this may signal a relapse. However, not every patient with this reconstitution relapses, suggesting a restoration of immune tolerance.10

Tumor necrosis factor α inhibitors have also been studied as adjuvant therapy as well in pemphigus. However, these agents may not be as successful in inducing remissions and the role of TNF-α in pemphigus is still not well understood.2 While IL-4 has been shown to play a major role in the pathogenesis of pemphigus and currently there are medications that block IL-4, such as dupilumab, no studies evaluating its role in the treatment of pemphigus have been published.5

Expert consensus panels have convened to define goals for treating patients with pemphigus as well as the doses required before considering a treatment to be a failure.9,12 Per such consensus, “disease control” was defined as no new lesions forming and established lesions improving over several weeks. CS doses should be maintained until no new lesions have developed for at least 2 weeks and most erosions have healed.9,12 Doses of 1.5 mg/kg of prednisone or an alternative CS equivalent should be used daily for 3 weeks with or without an adjuvant before a patient has been deemed to have failed treatment. Failed adjuvant doses are defined as 12 weeks of daily oral regimens of 2mg/kg of cyclophosphamide, 2.5 mg/kg of azathioprine, 3 grams of mycophenolate mofetil, or a weekly dose of methotrexate at 20 mgs.12

European guidelines have since recommended that all patients with pemphigus be treated with prednisone initially. Second-line therapy involves the addition of azathioprine, mycophenolate mofetil, or mycophenolic acid as an adjuvant. Third-line therapy is the replacement of the failed adjuvant with an anti-CD20 antibody, IVIG, immunoadsorption, cyclophosphamide, dapsone, or methotrexate.9 An alternative proposed algorithm included starting all pemphigus patients with CS and an adjuvant initially. If the treatment fails after 3 months of therapy the adjuvant therapy should be replaced with rituximab at 4 weekly doses of 375 mg/m². For patients with PNP, CS with rituximab as an adjuvant are recommended as first line therapy, often due to the concurrent Non-Hodgkin lymphoma.13

CONCLUSION

Despite the rarity of pemphigus in the general population, research continues to better elucidate the mechanisms underlying this group of diseases. Treatment regimens with long-term remissions and new medications are being evaluated as potential treatment options.

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ABSTRACT
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired immune-mediated disorder characterized by weakness and sensory deficits that can lead to significant neurological disability. The diagnosis is based on a combination of clinical examination findings, electrodiagnostic studies, and other supportive evidence. Recognizing CIDP and distinguishing it from other chronic polyneuropathies is important because many patients with CIDP are highly responsive to treatment with immunosuppressive or immunomodulatory therapies. This review summarizes the clinical features, diagnosis, and current treatment strategies for CIDP.

KEYWORDS: chronic inflammatory demyelinating polyradiculoneuropathy, CIDP, polyneuropathy, immune-mediated neuropathy

INTRODUCTION
Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired, immune-mediated disorder characterized by progressive symptoms of proximal and distal muscle weakness, often accompanied by sensory deficits. CIDP is a common, albeit frequently underdiagnosed condition with an estimated prevalence of 1 to 2 per 100,000 adults. Distinguishing CIDP from other chronic sensorimotor polyneuropathies is imperative as numerous therapeutic options are now available.

CLINICAL FEATURES
In adults, peak incidence occurs at 40-60 years of age with a slight male predominance. Classic presentation of CIDP is slow progression of both proximal and distal muscle weakness, often accompanied by sensory deficits. CIDP is a common, albeit frequently underdiagnosed condition with an estimated prevalence of 1 to 2 per 100,000 adults. Distinguishing CIDP from other chronic sensorimotor polyneuropathies is imperative as numerous therapeutic options are now available.

PATHOGENESIS
CIDP is an immune-mediated disorder generated from both cellular and humoral immune responses that are directed against peripheral nerve antigens, leading to demyelination and often secondary axonal loss. Studies of the pathogenesis of CIDP suggest that activated T lymphocytes invade the peripheral nervous system through derangement of the blood-nerve barrier. Once within the peripheral nervous system these activated T cells generate pro-inflammatory cytokines and produce cytotoxic activity against myelin. The myelin sheath is composed of numerous proteins, many of which are being investigated as possible targets for antibody responses in CIDP. Potential auto-antigens include myelin protein zero, myelin basic protein, connexin 32, and...
gangliosides. Overall, the mechanisms for these immune responses and the precise peripheral nerve antigens that are targeted have not been fully elucidated. Further research may assist in defining subtypes of disease and how they respond to particular treatments. For example, recent research has demonstrated that patients with antibodies against paranodal proteins contactin-1 (CNTN1) and neurofascin-155 (NF155) comprise a specific phenotype of CIDP that is refractory to first line therapies.

**DIAGNOSTIC WORK-UP**

**Diagnostic criteria**
As CIDP has become better recognized, researchers and professional societies have proposed various diagnostic criteria based on clinical features, specific electrodiagnostic criteria, and ancillary studies including nerve biopsy or lumbar puncture. Unfortunately, consensus is lacking. Review of the details of the various diagnostic criteria and their differences is outside the scope of this review. In general, the diagnosis of CIDP is primarily based on clinical presentation and electrodiagnostic studies, whereas CSF analysis and histologic studies provide additional supportive data in selected cases.

**Nerve conduction studies and Electromyography (EMG)**
Electrodiagnostic studies are key for determining if the underlying pathology is demyelinating or axonal. Hallmark findings of a demyelinating disorder in a nerve conduction study may include evidence of conduction block, prolonged distal latencies, slowing of conduction velocity, or absent/delayed F responses. The pattern of demyelination seen on these studies may be patchy or multifocal, in contrast to hereditary demyelinating polyneuropathies such as Charcot-Marie-Tooth disease, where demyelination is more uniform and conduction block is not seen. The needle EMG may reveal signs of secondary axonal loss.

**Lumbar Puncture**
Similar to AIDP, in CIDP there may be elevation of CSF protein with a normal cell count (albuminocytologic dissociation). Sampling of the CSF is not necessary in every patient suspected to have CIDP but may help further support the diagnosis in certain cases. Finding a pleocytosis in the CSF should prompt consideration of alternative diagnoses.

**Nerve biopsy**
A nerve biopsy may be considered in the workup of CIDP; however the diagnostic value is controversial. In patients with classic CIDP, the hallmark pathology includes demyelination and re-myelination changes, however this is only seen in about one-half to two-thirds of biopsies. Other findings that may be seen include nerve edema, nerve fibrosis, and inflammatory infiltrates. Unfortunately, the most prominent abnormalities in CIDP may lie in the proximal nerve segments or roots, which are not amenable to biopsy, and secondary axonal changes may obscure the underlying demyelinating process. However, nerve biopsies can be useful to identify or exclude other etiologies including amyloid or vasculitic, toxic, or hereditary neuropathies.

**Imaging findings**
MRI studies of CIDP patients may show gadolinium enhancement or enlargement of the nerve roots or the lumbosacral/brachial plexi, thought to reflect chronic inflammation and demyelination/re-myelination. In addition, advanced neuromuscular ultrasound techniques are now being investigated for utility in the diagnosis of CIDP, though ultrasound is still experimental in its applications for polyneuropathy.

**Other laboratory workup**
The differential diagnosis of CIDP is broad. Depending on the clinical scenario, a variety of laboratory studies may be considered to rule out neuropathy from other causes, including (but not limited to) toxicology screen, hemoglobin A1c, thyroid function studies, hepatitis profile, HIV antibody, serum immunofixation, Lyme titers, vasculitic markers, and angiotensin converting enzyme. Hereditary neuropathies, in particular the demyelinating forms of Charcot-Marie-Tooth disease, must also be considered in the differential diagnosis, especially in cases where there is a family history of neuropathy.

**TREATMENT**
Treatment is aimed at stopping the inflammatory response to prevent further demyelination and secondary axonal injury. The mainstays of treatment for CIDP include corticosteroids (CS), intravenous immunoglobulin (IVIg), and plasma exchange.

CS have been used in the treatment of CIDP for many years. While there is no strong evidence from controlled trials for oral CS, they are used commonly in practice and with good effect. Initial treatment with oral prednisone is typically high dose at 60-100 mg per day. Once the patient is stabilized clinically the dose is slowly tapered. Unfortunately, CS cause many undesirable systemic side effects so alternative dosing regimens have been considered. Trials comparing pulsed dexamethasone to standard daily prednisolone therapy show no significant difference in efficacy. Another small study comparing IV methylprednisolone to oral prednisone and IVIG demonstrated no difference in efficacy and fewer side effects as compared to prednisone. Alternate day dosing of oral prednisone may also be considered. There is no clearly preferred regimen for CS administration in CIDP.

IVIg has proven to be an effective alternative to CS with generally fewer side effects. There are no strong guidelines regarding dosing and frequency of IVIG. Typically a loading dose of 2 g/kg is given over 2-5 days but subsequent maintenance therapy is variable and dependent upon how rapidly
the patient relapses. Maintenance doses may range from 0.4-2 g/kg given as frequently as every 3-4 weeks. Patients can be maintained on IVlg long-term but weaning or discontinuing IVlg may be considered after a period of clinical stability of about six months or more. As with the dosing, there are no universal guidelines for tapering or discontinuing the medication and it is done on an individual basis. Side effects of IVlg include increased risk of thromboembolic events, renal dysfunction, and aseptic meningitis. Subcutaneous immunoglobulin, administered weekly, is more cost-effective and may be a consideration for patients who do not tolerate IVlg well but more data is needed to establish whether it provides the same efficacy as the IV formulation.

Plasmapheresis is another treatment modality that has demonstrated efficacy in small trials. However, it is more time consuming and invasive than IVlg, requiring the placement of a central venous catheter rather than a peripheral intravenous line. It can be used as initial therapy in a patient with prominent weakness followed by other, less invasive immunotherapy, or in some cases may be used for long-term treatment.

**Refractory Cases**

First line therapy for CIDP typically consists of IVlg, CS, plasmapheresis, or some combination of these agents. Other treatments may be considered in patients with refractory disease but strong supportive data for their efficacy is generally lacking. Additionally, many of these second- and third-line agents pose the risk of rare but serious side effects and should be considered with caution.

Cyclophosphamide and cyclosporine A have both shown positive results in small case series. Unfortunately they also pose the risk of significant side effects and use should be considered with caution. A small study of azathioprine showed no benefit in patients on oral prednisone therapy though there may be anecdotal support for its use. Methotrexate has been reported to yield some benefit in case reports, but a randomized, placebo-controlled trial of oral methotrexate [adjuvant to IVlg or corticosteroid maintenance] demonstrated no significant clinical benefit.

Rituximab is another consideration in patients not responsive to traditional therapies but more research is needed to establish its potential benefit; so far a significant treatment effect has not been proven in CIDP. However, as described above, recent data may suggest that rituximab is beneficial in a subset of treatment-resistant patients with antibodies against node of Ranvier proteins CNTN1 and NF155. Limited data suggests that alemtuzumab may also offer an alternative to traditional therapies for patients with refractory illness but further studies are needed and its use is experimental at this time. There have been several trials of interferons [interferon-alpha 2a and interferon beta 1a] that did not demonstrate efficacy.

Experimental treatments such as peripheral blood stem cell transplantation, have not demonstrated safety or efficacy to date. There is little data regarding non-pharmacological interventions such as regular exercise but physical therapy referral should be considered for patients with CIDP for gait training and fall prevention when clinically indicated.

**Conclusions**

Recognition of CIDP in a patient presenting with chronic neuropathy is crucial because treatments such as CS, IVlg, plasmapheresis, and other alternative agents may yield significant benefit with increased quality of life and reduction in disability. Future research is needed to establish the optimum treatment doses and durations for established therapies and to further investigate the utility of the alternative, less well-studied agents.

**References**


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Autoimmune Cytopenias: Diagnosis & Management

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ABSTRACT

The autoimmune cytopenias are a related group of disorders in which differentiated hematopoietic cells are destroyed by the immune system. Single lineage disease is characterized by the production of autoantibodies against red cells (autoimmune hemolytic anemia [AIHA]), platelets (autoimmune thrombocytopenia [ITP]) and neutrophils (autoimmune neutropenia [AIN]) whereas multilineage disease may include various combinations of these conditions. Central to the genesis of this disease is the breakdown of central and/or peripheral tolerance, and the subsequent production of autoantibodies by both tissue and circulating self-reactive B lymphocytes with support from T helper lymphocytes. These disorders are classified as primary (idiopathic) or secondary, the latter associated with an underlying malignancy, systemic autoimmune disease, infectious disease or a specific drug. Non-specific immunosuppression with corticosteroids remains the first-line therapy for many of these disorders, and although associated with high response rates, is compromised by significant toxicity and high relapse rates. Management of patients with chronic refractory autoimmune cytopenias who have failed first-line and second-line (cytotoxic immunosuppressant therapy and or splenectomy) is particularly complex, with definitive treatment in select patients requiring hematopoietic stem cell transplantation. Given the toxicity concerns of non-selective immunosuppressants, development of therapeutic regimens that avoid steroids has progressed rapidly in recent decades.

KEYWORDS: autoimmune cytopenias, WAIHA, CAD, ITP, AIN

INTRODUCTION

Failure to maintain self-tolerance is the dominant pathophysiological mechanism binding the autoimmune cytopenias, a group of disorders characterized by the immune mediated destruction of differentiated hematopoietic cells. Central tolerance is governed by apoptosis of autoreactive cells upon binding to self-antigen (negative selection), which occurs early in B and T cell differentiation in the bone marrow and thymus, respectively. In contrast, the active process of peripheral tolerance, is driven by CD4+/CD25+ regulatory T cells (Tregs) and CD8+ suppressor T lymphocytes which maintain anergy or suppression against self-antigens. Numerous mechanisms to account for central and peripheral tolerance breakdown in the context of autoimmune cytopenias have been proposed. The emergence of “forbidden clones” as proposed by Burnett more than sixty years ago, hinges on the persistence of self-reactive clones that should have been deleted via central tolerance, and may play a role in autoimmunity seen in lymphoproliferative diseases or polyclonal lymphocyte activation in viral infection. Molecular mimicry in the context of viral, bacterial and mycoplasma infections may also result in the initiation and acceleration of autoimmunity due to the presence of common antigenic epitopes in proteins and carbohydrates, particularly on the surface of red blood cells. Additional mechanisms to account for the failure to maintain self tolerance include neo-antigen generation by environmental agents or drugs, as observed in drug-induced AIHA, and immunoregulatory disturbances stemming from the alteration of cytokine networks. Interestingly, although autoimmunity is commonly thought to arise from the interplay between environmental factors and genetic predisposition, the HLA linkages documented for various organ and systemic autoimmune diseases such as type-1 insulin-dependent diabetes, pemphigus vulgaris, systemic lupus erythematosus, rheumatoid arthritis, etc., have not yet been clearly demonstrated for the autoimmune cytopenias.

AUTOIMMUNE HEMOLYTIC ANEMIAS

Pathogenesis

Autoimmune hemolytic anemia (AIHA) is defined by the destruction of mature red blood cells (RBCs) by anti-RBC autoantibodies produced by autoreactive B lymphocytes facilitated as otherwise by complement. Autoantibodies can result in erythrocyte destruction via numerous mechanisms including, a) phagocytosis of erythrocytes opsonized by autoantibodies and complement by activated macrophages, b) direct erythrocyte osmotic lysis through complement fixation and sequential activation of the membrane attack complex (MAC), and c) antibody-dependent cell-mediated cytotoxicity (ADCC) mediated by cytotoxic CD8+ T cells and natural killer (NK) cells that carry membrane receptors for the Fc portion of bound immunoglobulin G (IgG). ADCC and erythrophagocytosis preferentially occur in the
spleen and lymphoid organs, whereas complement mediated destruction is primarily intravascular or occurs in the liver. AIHAs are divided into warm and cold types according to the thermal characteristics (reactivity at 37°C or 4°C) of the predominant autoantibody formed, which in large part is predicated on the antibody class (IgG versus IgM), and the chemical characteristics of the epitope (protein or carbohydrate).

**WARM AUTOIMMUNE HEMOLYTIC ANEMIA**

**Clinical Features & Laboratory Findings**

Optimal reactivity of the autoantibody at 37°C (mainly IgG1 and IgG3 subclass), defines warm autoimmune hemolytic anemia (WAIHA) which can affect all age groups and accounts for 80-90% of adult cases of AIHA. Clinical and laboratory features are shown in Table 1. In vivo binding of antibody and/or complement to the red blood cell (RBC) surface can be detected in a direct Coomb’s or antiglobulin test (DAT). In nearly half of all WAIHA cases, these pan-reactive autoantibodies exhibit specificity for Rb protein epitopes. [5]

**Management**

Transfusion of allogeneic red cells for rapid symptomatic improvement of hypoxic anemia along with controlled non-specific immunosuppression with pharmacologic doses of corticosteroids represents front-line therapy. Initial hemoglobin stabilization and prompt symptomatic improvement is observed in up to 70-80% of patients. However, disease relapse after steroid-induced remission is common. [6] Corticosteroid non-responders can be managed with other non-specific immunosuppressants such as cyclosporin A, azathioprine and cyclophosphamide. [7] Although splenectomy has played a dominant historical role in the management of WAIHA, with the first series of patients (n = 28) described by Chertkow and Dacie in 1955, [8] data regarding durable remission remains unclear with an approximate response rate of 38-70% in patients with WAIHA. [9] Reombinant erythropoiesis-stimulating agents (ESA) represent an alternative promising treatment modality that may be more widely employed in the future, [10,11] and high dose IVIG, although less successful than in ITP, may be efficacious in some non-responder cases. [12]

Targeted therapy with Rituximab, a potent, humanized monoclonal antibody directed against CD20 on pre-B cells, mature B lymphocytes, and immature plasma cells, has been increasingly used as second-line therapy in relapsed or refractory cases. Binding of rituximab to CD20-positive cells results in B-lymphocyte depletion via a combination of apoptosis, complement activation and antibody-dependent cell cytotoxicity. [13] Small case series have supported the efficacy and safety of this drug in children and adults with WAIHA with durable responses of up to 3 years. [14,15] Response rates of 33–57% with complete remission in 29–55% have been reported in an evidence-based focused review, [16] with the beneficial effect greatest in neonates and children compared to adult patients with WAIHA. [14,15,17] Long-term side effects remain to be explored, yet mild infusion reactions including hypotension and fever are the most common complications of rituximab with a very low incidence of serious infection. [18] A battery of additional treatment modalities in various stages of the investigational and licensure pipeline include such drugs as alemtuzumab (anti-CD52), bortezomib, kinase inhibitors and IgG-specific endoglycosidase EndoS. [19-22]

**COLD ANTIBODY AUTOIMMUNE HEMOLYTIC ANEMIAS**

**Pathogenesis**

Cold antibody autoimmune hemolytic anemias are serologically characterized by autoantibodies with optimal reactivity at 4°C, with the majority of cases being either cold agglutinin syndrome (CAS) or paroxysmal cold hemoglobinuria (PCH). The autoantibodies in primary CAS are monoclonal IgM, and polyclonal IgM in secondary CAS due to infectious diseases such as Mycoplasma pneumoniae and infectious mononucleosis. The polyclonal antibodies produced in response to these infections typically demonstrate specificity to the RBC blood group antigens I and i, respectively. The antibody specificity in PCH is a polyclonal IgG immunoglobulin directed toward the P blood group antigen.

<table>
<thead>
<tr>
<th>Table 1. The Autoimmune Cytopenias</th>
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<tbody>
<tr>
<td><strong>Disorder</strong></td>
</tr>
<tr>
<td>Warm Autoimmune Hemolytic Anemia</td>
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<tr>
<td>Cold Autoimmune Hemolytic Anemia</td>
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<tr>
<td>Autoimmune Thrombocytopenia</td>
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<tr>
<td>Autoimmune Neutropenia</td>
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**ADVANCES IN AUTOIMMUNE DISEASES**
This bi-phasis hemolysin (Donath-Landsteiner antibody) reacts with RBCs in the peripheral circulation when the temperature drops below 20°C, and initiates complement fixation. Upon returning to the warmer central circulation, complement mediated erythrocyte osmotic lysis ensues. (23)

Clinical Features & Laboratory Findings
Clinical features are shown in Table 1. CAS typically manifests as moderate chronic hemolytic anemia in middle-aged or elderly patients, often with cold exacerbation of signs [acrocyanosis of the extremities], splenomegaly, anemia and mild jaundice. Prognosis is generally fair although significant mortality has been described. (24) PCH is characterized clinically by acute hemolytic anemia often with hemoglobinuria, predominantly in children with a history of a recent viral illness. Although PCH typically follows a mercurial, acute, often severe course, prognosis is excellent with the majority of cases spontaneously resolving within a few days to several weeks following onset. The direct Coomb's test will be positive for complement (C3) and negative for IgG. Erythrophagocytosis of complement sensitized cells can be observed in the peripheral blood films of up to 80% of young children with acute transient PCH (Figure 1).

Figure 1. Peripheral blood smear of a biphasic hemolysin positive case of paroxysmal cold hemoglobinuria (PCh) in a four-year-old child, exhibiting prominent monocytic erythrophagocytosis with occasional spherocytes.

Management
Cold exposure avoidance, red cell transfusion for hypoxic anemia, and immunosuppression with the alkylling agents chlorambucil and/or cyclophosphamide represent front-line therapy for CAS. B lymphocyte depletion with rituximab to remove the pathologic clonal B cells, has been investigated in case reports, small retrospective series and phase 2 trials. (25,26) In these studies, rituximab monotherapy achieved partial responses in greater than 50% of patients with CAS, complete responses in 5% and disease improvement in those who had previously received rituximab. However, median duration response of 11 months and failure rates of 40-50% remain impediments to universal implementation of this drug in the treatment of CAS. In PCH, the severe acute intravascular hemolysis (Figure 2), may necessitate transfusion of red blood cells along with supportive care provided in a heated room.

Figure 2. Three plasma samples collected from the same patient with PCH at 0 (A), 3 days (B), and 4 days (C) after admission. Hemoglobinemia resulting from intravascular hemolysis is most readily apparent in the plasma sample collected on presentation (day 0), which quickly resolved in the ensuing week. Hemoglobin concentrations (mg/dL): A = 83; B = 43; C = 28 (normal < 2 mg/dL).

Autoimmune Thrombocytopenia
Pathogenesis
Immune mediated destruction of platelets along with attenuated platelet production characterize ITP (27) which is mediated in part by anti-platelet IgG and T-cell subset abnormalities. (28,29) Using antigen-specific assays that measure autoantibodies capable of binding to platelet surface glycoproteins, anti-platelet autoantibodies can be detected in only 50-60% of ITP patients. (30) A limited number of B-cell clones produce these antiplatelet antibodies as a result of antigen-driven somatic mutation. (31) Platelets coated with autoantibody are cleared in the reticuloendothelial system by phagocytosis and possibly complement-mediated lysis. (32) Hepatic clearance of platelets by an anti-GPIb-IX mediated Fc-independent mechanism involving the Ashwell-Morell receptor may also occur. (33) Furthermore, the lack of autoantibodies in many ITP patients has led to the discovery that cytotoxic CD8+ T lymphocytes can lyse platelets in vitro and impair megakaryocyte function. (34)

Clinical Features & Laboratory Findings
Autoimmune thrombocytopenia (ITP) is the most common of the autoimmune cytopenias with an incidence of five out of 100,000 children per year and two out of 100,000 per year in adults. ITP may be primary, secondary to autoimmune disease, infection (CMV, HIV, Hepatitis C, Helicobacter pylori) and malignancy, drugs (35) or occur in association
with AIHA [Evan’s syndrome]. Common clinical features are listed in Table 1. Adults tend to run a chronic course, whereas shorter disease duration (approximately 6 months) and much higher spontaneous remission rates occur in children. Bone marrow biopsy indicated in patients > 60 years of age to exclude an underlying B cell malignancy may reveal normal or increased megakaryopoiesis. [36]

Management
Corticosteroid taper and intravenous immunoglobulin represent front line therapy for ITP, with approximately 70-80% response rate in newly-diagnosed, previously untreated ITP patients. [37] However, recurrence of thrombocytopenia in the majority of patients, necessitates additional intervention. Optimal second line therapy remains uncertain, although traditionally splenectomy for steroid refractory patients has been employed at the risk of post-operative complications and 1% mortality due to septicemia. [38] High-dose dexamethasone instead of prednisone has been advocated in adults as a different strategy to avoid second-line therapy altogether. Numerous alternative strategies such as B-cell depletion with the monoclonal antibody rituximab, anti-D immunoglobulin, thrombopoiesis-stimulating agents and Fc receptor blockade have been investigated. Retrospective and prospective single-arm trials have shown a beneficial effect of rituximab therapy in adult and childhood ITP, [39] which may be boosted with combinatorial regimes involving rituximab and dexamethasone, [40] or even triple therapy with the inclusion of cyclosporine [TT4]. [41] Rapid platelet responses have been observed with the thrombopoietin [TPO] receptor agonists (romiplostim and eltrombopag), although medication discontinuation is often followed by a platelet count drop to pretreatment levels. [42,43] In non-splenectomized Rhesus positive individuals with ITP, anti-D immunoglobulin therapy may be similarly efficacious as conventional treatments through the saturation of macrophage Fc receptors by opsonized red blood cells. [44] Targeted Fc receptor blockade with monovalent anti-Fcy receptor/albumin fusion proteins and/or neutralization of autoimmune IgG Fc by soluble FcRs is also being pursued. [45,46] Inhibition of platelet glycoprotein desialylation with the antiviral sialidase inhibitor, oseltamivir phosphate, has resulted in significant platelet count increases in anti-GP1b autoantibody positive chronic ITP patients refractory to all other conventional therapies, representing a promising antigen specific area of future research. [47] Platelet transfusion is usually reserved only for patients with acute life-threatening bleeding (retinal or intracranial hemorrhage) due to the rapid clearance of infused platelets.

**AUTOIMMUNE NEUTROPENIA**

Pathogenesis
Autoantibodies directed against neutrophils are primarily responsible for the rare entity autoimmune neutropenia (AIN). AIN be primary or secondary to viral infections, drug-induced mechanisms, hematological malignancies such as large granular lymphocyte leukemia, autoimmune diseases and primary immune deficiency syndromes. Antigens in the polymorphic human neutrophil antigen system (HNA), particularly HNA-1 and HNA-4, located on the FcγRIIb (CD16) and CD11b molecules respectively, are the primary targets of anti-neutrophils antibodies which can be demonstrate in up to 70% of cases. [48] Cell-mediated destruction of granulocytes may also occur due to inhibitory CD8+ cytotoxic T-cells present within the marrow space.

Clinical Features & Laboratory Findings
As with other autoimmune cytopenias, the natural history of AIN varies between children and adults, with a relatively benign course and spontaneous remission within 6-24 months commonly occurring in children, in contrast to a more pronounced, chronic course in adults. Upper respiratory tract infections, skin sepsis, recurrent fevers, otitis media in children and chronic tiredness in adults may all be presenting signs.

Management
Front line therapy with recombinant human granulocyte colony stimulating factor (rhG-CSF) can be used in the immediate treatment of severe infections as well as for infection prophylaxis at a decreased dosing schedule. [49] Immunosuppression, intravenous immunoglobulin and splenectomy have produced variable to disappointing results in the treatment of AIN. Rituximab likewise, has met with limited efficacy in this disorder, presumably due to the central role of the inhibitory CD8+ cytotoxic T cells. [50]

**SUMMARY**

Immune mediated destruction of hematopoietic cells characterizes the autoimmune cytopenias. The complexity of these cases indicate that referral to a hematologist is indicated in nearly all cases. Viral infections, autoimmune diseases, drugs, solid tumors and hematopoietic malignancies underlie many of the cases of secondary autoimmune cytopenias. Natural history variation between children and adults generally predicts higher rates of spontaneous remission and shorter disease duration in children. Non-specific immunosuppression with corticosteroids represents front-line therapy for many of these disorders yet active investigation into steroid sparing regimes has uncovered multiple new treatment modalities. Notably, autoreactive B lymphocyte depletion via targeted therapy with the humanized, chimeric monoclonal anti-CD20 antibody, rituximab, has provided durable responses in AIHA and ITP, whereas the mammalian target of rapamycin inhibitor, sirolimus, may provide safe and efficacious mono-therapy treatment for patients with refractory autoimmune multilineage cytopenias. [51] Recombinant erythropoiesis-stimulating agents may in the future become standard therapy in WAIHA, and newly vetted targets to treat ITP include monovalent Fc receptor blockade and combinatorial therapy including rituximab, dexamethasone, thrombopoietin receptor analogues and cyclosporine.
References


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Conflicts of Interest

None.

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Fibromyalgia Syndrome, A Geriatric Challenge

JULIO C. DEFILO-DRAIBY, MD; JOHN S. PAGE

INTRODUCTION

Fibromyalgia syndrome (FMS) is a syndrome characterized by waxing and waning widespread musculoskeletal pain, muscle stiffness, fatigue and sleep disturbance, all of which result in functional impairment without an identifiable cause. The US prevalence is 2%, with a female predominance [18]. FMS incidence increases with age; it has been found to be as high as 7% between 60–79 years [16]. Its peak onset is between 30–50 years of age [14, 19]. Given the high prevalence of multiple morbidities in older adults, many of which share symptoms with FMS, diagnosis can be challenging. Co-morbidities (COPD, CHF, renal insufficiency, anemia, mood disorders, dementia, rheumatologic diseases, osteoporosis, malnutrition) often interact with, precipitate or exacerbate FMS. Therapeutic options are limited, not only due to medication side effects but also due to impaired patient function, which may prevent participation in non-pharmacologic interventions, such as aerobic exercise or cognitive behavioral therapy.

In elderly patients, FMS is usually diagnosed after multiple medical visits and costly diagnostic testing. The etiology is not known, but there are several theories concerning the cause of FMS, including abnormalities in pain processing and neurotransmitter release (low serotonin, elevated substance P) that provoke increased perception of pain, often with non-painful stimuli. Additional theories on its origin include muscle disease, stage 4 non-rapid eye movement sleep disorders and psychological factors [14]. The revision to the 1990 classification criteria by The American College of Rheumatology in 2010 incorporated a new case definition that includes widespread pain and symptoms of fatigue, waking up unrefreshed, cognitive complaints and somatic symptoms. These revisions were implemented to improve the clinical diagnosis of FMS, emphasizing that the old criterion of 11 out of 18 tender points is no longer necessary. Instead, with these revised guidelines the clinical diagnosis of FMS is made when the following 3 conditions are met [19]:

1. The Widespread Pain Index (WPI) ≥ 7 and the Symptom Severity Score [SS] ≥ 5, or the WPI is 3-6 and the SS ≥ 9;
2. Symptoms have been present at a similar level for at least 3 months;
3. The patient does not have a disorder that would otherwise explain the pain.

Ascertainment: WPI notes the number of areas in which the patient has had pain over the last week, scoring between 0 and 19. (Shoulders, upper and lower arms, hips, upper and lower legs, jaw, chest, abdomen, upper and lower back, and neck. Left and right limbs are counted individually).

SS takes into consideration the degree of unrefreshed sleeping, fatigue and impaired cognition of the patient. Each of these three symptoms is scored from 0–3, depending on the severity over the past week. {0: no problem, 1: mild, 2: moderate 3: severe}. The SS also factors in the extent (severity) of general somatic symptoms, e.g., muscle pain, irritable bowel syndrome, weakness, headache, cramps, blurred vision, dry eyes, hives. {0: no symptoms, 1: few symptoms, 2: moderate symptoms, 3: many symptoms}.

SS is the sum of the severity of the three symptoms (fatigue, unrefreshed sleep and cognitive symptoms) plus the extent (severity) of somatic symptoms in general. The final score ranges from 0–12.

APPROACHES TO TREATMENT IN THE ELDERLY PATIENT

To properly manage FMS, focus should be on predisposing and precipitating factors, prevalent symptoms and patient preferences. Research on the effectiveness of treatment of FMS is limited, and optimal treatment for elders remains unknown. Multiple review articles recommend a stepwise approach, combining pharmacological and non-pharmacological interventions. Since the etiology remains unclear, therapy is focused on the treatment of symptoms. Knowing precipitating factors and how to avoid them becomes all-important in the prevention of flares. Some known triggers include emotional stress, cold weather, illness and exertion.

Elderly patients may find it challenging to adhere to exercise or physical medicine and rehabilitation (PM&R). Additionally, for many it proves difficult to tolerate pharmacological intervention due to various side effects or a lack of efficacy. Because of these obstacles, a shared understanding of the goals of treatment by both patient and physician is crucial. Treatment targets include underlying causes, symptom management and activities of daily living (ADLs), knowing that not all symptoms can be eliminated. Patients also need to monitor symptoms and report them. Intact cognitive function is essential; when impaired, management becomes more challenging.

Currently 3 medications are FDA-approved for the treatment of FMS; duloxetine, pregabalin and milnacipran [9].
addition, multiple other medications and non-pharmacological interventions have been studied, the extent and rigor of evidence varies widely, and some should be avoided or used with caution in the treatment of elders.

**FDA-APPROVED MEDICATIONS**

A comparative analysis was done in 2010 of the three medications approved by the FDA for FMS; subjects were 30–50 years of age [9]. The author presented comparative data on the short-term (6-month) efficacy and harms of duloxetine, milnacipran, and pregabalin in FMS [9]. Among the 3 medications, there were no differences in pain control or dropout rate due to side effects. If depression was the predominant symptom, duloxetine showed the best response. If fatigue was predominant, milnacipran or pregabalin were better choices. In this analysis, milnacipran did not have any effect on sleep, duloxetine did not affect fatigue, and pregabalin did not affect depressive symptoms [9]. When choosing these medications for elderly patients, slow titration should be used to reach the minimum effective dose.

**PHARMACOLOGICAL INTERVENTION**

It is of great importance to take the minimum effective dose because of the wide profile of side effects that accompany many of the medications given to ameliorate the symptoms of FMS. The Beers Criteria for Potentially Inappropriate Medication in Older Adults is particularly useful, as the long-term results and applications of these medications for the elderly FMS patient remain unknown. In some cases, the side effects outweigh the therapeutic benefit; e.g.: NSAIDs. The administration of tramadol with acetaminophen, taken at average doses of 151 mg/d and 1238 mg/d respectively, has been shown to be effective in treatment for some of the pain associated with FMS [3]. Analgesics can be very beneficial initially, as we introduce other interventions to the management of symptoms; however, long-term use of pain medications is rarely a good solution, especially in an older population. Tramadol may increase the risk of seizure when combined with other drugs for FMS, and may increase the risk of serotonin syndrome when administered with SSris or SSNRIs [14]. SSris and SSNRIs alone have been shown to be effective not only in treating the depressive symptoms of FMS, but also other symptoms as well.

Although no SSRI is FDA-approved for the treatment of FMS, citalopram, paroxetine, and fluoxetine have been shown to have therapeutic effects in non-depressed patients but the mean age of subjects in the following studies was only 50. Citalopram in doses of 20–40 mg/d improved well-being without affecting other symptoms over a 4-month follow-up [1]. In elders, no more than 20 mg/d is recommended because of risk of QT prolongation per FDA DrugSafety Communication. Paroxetine, administered at a mean dose of 40 mg/d, was found useful in treating FMS symptoms in a randomized trial [12]. Fluoxetine has also been shown to be beneficial in the treatment of all aspects of FMS in multiple studies, with dosages ranging from 20–50 mg/d. Duloxetine and milnacipran are SSNRIs that are FDA-approved for use in FMS. Duloxetine was approved on the basis of its ability to reduce

### Table 1. Medications used in Fibromyalgia Syndrome

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended dose</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Gabapentin</td>
<td>100-600 mg daily Max dose 1800 mg daily</td>
<td>Target symptoms: Fatigue and pain. Titrate slowly. May cause sedation and dizziness. Dose should be adjusted for renal failure.</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>150-300 mg daily Max dose 450 mg daily</td>
<td>Target symptoms: Pain, fatigue and sleep. Sedation and confusion. Avoid in narrow angle glaucoma. Recommend baseline EKG and avoid if QT prolongation.</td>
</tr>
<tr>
<td>Tricyclic antidepressants (TCA)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>10-50 mg nightly</td>
<td>Target symptoms: Pain, fatigue and sleep. Sedation and confusion. Avoid in narrow angle glaucoma. Recommend baseline EKG and avoid if QT prolongation.</td>
</tr>
<tr>
<td>Serotonin reuptake inhibitors (SSRIs)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>5-60 mg daily</td>
<td>Target symptoms: Depression. Better tolerability than TCA</td>
</tr>
<tr>
<td>Citalopram</td>
<td>10-20 mg daily</td>
<td>Insomnia. Hyponatremia. Fluoxetine has long half life.</td>
</tr>
<tr>
<td>Serotonin norepinephrine reuptake inhibitors (SNRI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>25-100 mg daily</td>
<td>Target symptoms: Depression and pain. Avoid in those with uncontrolled hypertension, liver disease and open angle glaucoma.</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>30-60 mg daily</td>
<td>Target symptoms: Depression and pain. Avoid in those with uncontrolled hypertension, liver disease and open angle glaucoma.</td>
</tr>
<tr>
<td>Milnacipran</td>
<td>25-200 mg daily</td>
<td>Target symptoms: Fatigue and pain. Contraindicated with monoamine oxidase inhibitors and open angle glaucoma.</td>
</tr>
<tr>
<td>Analgesics</td>
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</tr>
<tr>
<td>Tramadol</td>
<td>25-50 mg every 6 hrs as needed</td>
<td>Target symptoms: Pain. May cause sedation and confusion. Avoid in patients with seizures. May cause serotonin syndrome in combination with SSRI or other antidepressants. Dose adjustment for renal failure.</td>
</tr>
<tr>
<td>Muscle relaxants*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclobenzaprine</td>
<td>5-10 mg nightly</td>
<td>Target symptoms: Pain, sleep and mood. Sedation. Similar side effects to TCA.</td>
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</table>

pain, fatigue, and depression. Recent studies have found that it is no more effective when administered at 120 mg/d compared to 60 mg/d [6]. It has a higher incidence of nausea and headache than the other two approved medications [9, 10]. Milnacipran, approved for its efficacy in improving pain, fatigue, and sleep quality, does not appear to have such limiting side effects. Twice-daily dosage is superior for pain control, and can be titrated up to a total of 200 mg/d. Two of three randomized, controlled trials showed improvement in cognition. Pain and fatigue improvements were seen within one week in responders to milnacipran. Milnacipran has no effect on depressive symptoms [2, 7, 14]. Nortriptyline, a tricyclic antidepressant (TCA), has been minimally studied but 10–30 mg/d before bedtime is a safer option for the elderly patient when compared to other TCAs; of note, nortriptyline is a prominent potentially inappropriate medication according to the Beers Criteria [5, 10].

NOTE: A 2012 systematic review and meta-analysis of the role of antidepressants in the treatment of FMS noted that although a small number of patients experienced substantial symptom relief, the majority of patients experienced intolerable adverse effects and only modest relief of symptoms. The conclusion was that physicians and patients should be realistic about the potential benefits of antidepressants in FMS [10]. Anticonvulsants are another class of drugs that have some utility in the improvement of symptoms of FMS in the elderly, although little research has been done in an older population [8]. Gabapentin was shown in a 2007 randomized, double-blind, placebo-controlled trial to be useful in the treatment of pain and also improved sleep and quality of life. Higher doses produced excess adverse effects, especially in older adults [8, 16]. Pregabalin, unlike gabapentin, is FDA-approved for FMS and has more data supporting its use. A recent meta-analysis that included 5 RCTs showed that doses ranging from 150–600 mg/d were effective in improving pain, sleep, and quality of life. Like gabapentin, higher doses result in more adverse effects in older adults – accordingly, the dose should be titrated slowly to the minimum effective dose [8, 16].

For patients struggling with side effects and contraindications, a low dose [1–4 mg/d] of cyclobenzaprine, although not FDA-approved, has been shown in clinical trials to cause significant improvements in pain, and depressive symptoms, without limiting side effects [5, 17]. In older adults, a low starting dose of 1–5 mg/d is recommended. In general however, muscle relaxants should be used as a last resort for the management of FMS symptoms in elderly patients, in accordance with the Beers Criteria. A 2004 meta-analysis showed that there were no improvements in fatigue or tenderness in studies that used doses of 10–30 mg/d; however, tenderness has been shown to improve with administration of 1–4 mg/d [5, 17]. Lower dosages have been shown to be beneficial, and have fewer side effects. Along with these improvements comes increased nights of restorative sleep [17].

**NON-PHARMACOLOGICAL APPROACHES TO TREATMENT**

**Patient Education**

Patient education is paramount in the control of FMS symptoms, beginning by acknowledging the disease and learning about its complexity. Clinicians need to work closely with patients to establish goals of treatment, and to encourage patients to report changes in symptoms [4, 14].

**Exercise**

Multiple studies and systematic reviews demonstrate that supervised, paced aerobic exercises have positive effects on global well-being and physical function, and possibly on pain and tender points. Gradual increase in exercise intensity prevents exacerbation of the pain that ultimately could lead to patient non-adherence to the program or acute worsening of symptoms [16, 17]. Water-based exercise programs have also been shown to be helpful in improving tender points and sleep quality [4, 11].

**Cognitive Behavioral Therapy (CBT)**

In most studies, CBT improved pain-related behavior, self-efficacy, coping strategies and overall physical function, and are most effective when combined with comprehensive programs. There was no evidence in subjects above 50 years of age [7, 13, 15].

**Multi-component intervention and Multidisciplinary Approach**

A 2009 meta-analysis of 9 randomized controlled clinical trials that met the inclusion criterion of utilizing at least two non-pharmacological therapies [educational or psychological interventions and at least one exercise program], showed that multi-component therapy could effectively reduce pain, fatigue and depressed mood. It also showed that efficacy declines over time; long-term effects are inconclusive [7]. This major analysis, like every study noted above, may not be relevant to older adults as subject age was 30–50 years. Unfortunately, a non-pharmacological approach, including multi-component interventions, seems to lack conclusive results. Further research will be of utmost importance in targeting appropriate treatment [16].

**CONCLUSION**

Fibromyalgia-related physical disability and discomfort affects older adults profoundly. It is important to acknowledge that the complexity of symptoms and the lack of specific treatment make FMS challenging to manage. The evidence base in the FMS literature is limited to patients <50 years. The limited response to drug treatment in elderly patients, and their increased susceptibility to adverse effects, as well as baseline restriction in mobility make treatment even more challenging. Both the short-term and long-term effects of any treatment remain unknown. Accordingly,
individualized treatment programs are recommended. Recognizing treatment limitations, educating patients and implementing multimodal therapy is currently recommended to limit disease burden and disability.

References

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Fournier’s gangrene of the penis in a 12-year-old patient secondary to phimosis
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ABSTRACT
We report a case of Fournier’s gangrene in a 12-year-old boy from St. Boniface Hospital in Fond-des-Blancs, Haiti. Fournier’s gangrene, a fulminant necrotizing fasciitis of the penis and scrotum, is a rare and life-threatening infection that requires hospitalization, broad-spectrum antibiotics, and surgical debridement.1–3 It is usually associated with impaired cellular immunity due to systemic disorders such as diabetes and liver disease.4,5 This patient had none of those risk factors, but had severe, longstanding phimosis, for which circumcision had been recommended many years before. This case illustrates how lack of access to basic surgical care for an easily treatable condition leads to advanced presentation of a severe disease process.

KEYWORDS: Fournier’s gangrene in pediatric patient, necrotizing fasciitis of the penis, phimosis, global surgery, lack of access to surgery

CASE REPORT
A 12-year-old boy presented to St. Boniface Hospital with pain and swelling of the penis and scrotum and an inability to urinate for two days. On examination, the patient was noted to have severe phimosis with patchy necrosis and a grossly edematous penis and scrotum. The patient’s bladder was drained of 1100cc of urine with a suprapubic catheter. Laboratory analysis revealed a creatinine of 3.6. The patient was taken to the operating room for an emergency debridement. The foreskin and more proximal shaft skin were necrotic through Buck’s and into Dartos Fascia, and were debrided. The corpora cavernosa and spongiosum were intact. The area of debridement was irrigated with normal saline and Dakin’s solution, and packed with dressings soaked in Dakin’s. No damage to the urethra was observed, and a Foley catheter was placed to facilitate wet-to-dry dressing changes for two weeks.

The patient returned to the operating room two weeks later for a meshed 1:1 split-thickness skin graft to cover the remaining defect on the shaft of the penis.

DISCUSSION
Fournier’s gangrene (FG) is a life threatening disease of the perineum and genitalia in which a bacterial infection results in small vessel occlusion, gangrene of the overlying skin, and expansion of the necrotizing infection along fascial planes through bacterial enzymatic degradation.3,5 The portal of entry may be genitourinary, anorectal, or cutaneous, and causal organisms are usually normal flora that interact synergistically in a polymicrobial infection.5–7 Accordingly, FG is typically associated with conditions that impair host cellular immunity, such as diabetes mellitus, alcoholism, liver disease, HIV, chronic illnesses, and malignancy.4,5,8,7 It is rarely seen in children, and most reported pediatric cases have involved children younger than 3 months.6 The patient presented in this case did not have any of the commonly associated risk factors, but developed Fournier’s gangrene secondary to phimosis.

Phimosis is a condition in which inflammation and scarring of the foreskin leads to a permanently un-retractable prepuce that cannot be drawn back to reveal the glans penis.9,10 Narrowing of the foreskin orifice may compress the meatus, causing high-pressure flow that leads to inflammation of the periurethral tissues; in some cases, phimosis may lead to complete urethral obstruction.

Obstruction, inflammation, and penile edema may create an ischemic process prone to infection.12 The etiology of infection in this case cannot be confirmed due to the diagnostic limitations of the facility, but the authors suspect that phimosis and balanoposthitis led to obstruction and a subsequent urinary tract infection; leaking of infected urine into un-retractable foreskin led to cellulitis which soon progressed to Fournier’s gangrene.
Few cases of Fournier's gangrene secondary to phimosis have been described in the literature. While rare, these are usually seen associated with other more common risk factors for Fournier's gangrene. In this case, the patient's mother explained that he had been diagnosed with phimosis when he was two years old, and the parents were told that he needed circumcision and would be placed on a list for a visiting surgical team. However, the patient's family was never contacted and never returned to the hospital; the patient's increasingly stenotic foreskin led to complete urethral obstruction and gangrenous infection, ten years after his initial diagnosis of phimosis.

The Lancet Commission on Global Surgery estimates that 5 billion people worldwide lack access to surgical care when needed, including nine out of ten people in low-middle income countries (LMICs) like Haiti. This case is a striking example of how lack of access to basic surgical care transformed a relatively benign process (phimosis), into a devastating and life-threatening emergency (necrotizing fasciitis of the penis with complete urethral outflow obstruction) requiring multiple surgical procedures and producing permanent genital disfigurement.

References
9. Division of Paediatric Surgery, Department of Surgery, The University of Hong Kong, Queen Mary Hospital, Hong Kong, Chan, IH, Wong, KK: Common urological problems in children: prepuce, phimosis, and buried penis. Hong Kong Med J 2016;doi:10.12809/hkmj154645.

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Right in Front of Our Eyes: Evolution of Streptococcal Toxic Shock Syndrome with Ischemic Optic Neuropathy
SALAH ELHAMDY, MD; MAZEN AL-QADI, MD; TARO MINAMI, MD; MARGUERITE NEILL, MD

ABSTRACT

INTRODUCTION: Toxic shock syndrome occurs from dysregulation of host inflammatory responses. Toxin-producing strains of Group A streptococcus cause TSS. Ischemic optic neuropathy rarely complicates septic shock. We present a rare case of streptococcal pharyngitis complicated by septic arthritis and TSS with reversible blindness due to non-arteritic ischemic optic neuropathy.

CASE: A 28-year-old man drove to our emergency department with exudative pharyngitis. A rapid streptococcal test was positive. While awaiting oral penicillin, he became hypotensive refractory to IV fluids and developed knee effusion. The patient noted progressive dimming of his vision. Arthrocentesis yielded GAS. ICU course was complicated by ARDS but after 2 weeks the patient was weaned off vasopressors and the ventilator. He regained his vision and had no neurological sequelae. The patient’s GAS isolate was M protein gene [emm] type 1 and T type 1. He was followed in the IM clinic for 9 months post discharge with complete resolution of symptoms.

CONCLUSION: The rapidity of the development of shock is attributed to streptococcal exotoxins acting as superantigens. GAS type M1 is commonly associated with severe shock in TSS. The severe shock was the likely cause of his ischemic optic neuropathy. Early recognition and aggressive management of TSS are crucial to clinical outcome.

KEYWORDS: Toxic shock syndrome, TSS, Staphylococcus aureus, Group A streptococcus

INTRODUCTION

Toxic shock syndrome (TSS) is a severe illness caused by dysregulation of host inflammatory responses resulting in multi-organ failure. Toxin-producing strains of Staphylococcus aureus [S. aureus] or Group A streptococcus (GAS) cause TSS. Streptococcal pharyngitis is almost never associated with TSS. Ischemic optic neuropathy rarely complicates septic shock, particularly in young individuals. We present a rare case of streptococcal pharyngitis complicated by septic arthritis and TSS with reversible blindness due to non-arteritic ischemic optic neuropathy.

DISCUSSION

Toxic shock syndrome (TSS) is a toxin-related severe illness that occurs due to dysregulation of host inflammatory responses, causing hypotension and multi-organ failure.
Toxin-producing strains of *S. aureus* [including methicillin-resistant, MRSA] or Group A streptococcus (GAS) are the most common pathogens for TSS. Although uncommon, other bacteria, such as groups C and G β-hemolytic streptococci, *Clostridium* spp. and coagulase negative staphylococci may cause TSS as well. Furthermore, probable association with influenza infection has been described [1]. The annual incidence of invasive GAS infection has been estimated to be 1.4/100,000 population, of which TSS develop in 13% of patients [2]. Streptococcal TSS is primarily caused by skin and soft tissue infection [nearly 50%], followed by pneumonia. Approximately 15% of patients with TSS will have streptococcal bacteremia with no clear source. Streptococcal TSS is more common in patients who are younger than 50-years-old. Furthermore, chronic alcoholism, uncontrolled diabetes mellitus, varicella infection, and recent plastic surgery are recognized risk factors. Compared to staphylococcal TSS, most patients with streptococcal TSS have invasive syndromes such as necrotizing fasciitis, myonecrosis, or bacteremia. GAS causes TSS by producing superantigens, which are extracellular toxins that bypass antigen presenting cells, resulting in antigen-independent release of proinflammatory mediators and massive activation of T cells without major histocompatibility complex (MHC) class II restriction. Extensive inflammatory response and shock quickly ensue with widespread tissue damage and multi-organ dysfunction. Virulent factors responsible for invasive streptococcal disease and TSS include antiphagocytic proteins [called M proteins], cytotoxic toxins [A, B, C], and certain enzymes such as streptokinase and hyaluronidase. Among these factors, the M proteins [M1 and M3] and pyrogenic exotoxin A [80% of streptococcal TSS] are more likely to cause invasive GAS infection and TSS. The diagnosis of streptococcal TSS is made by fulfilling the diagnostic criteria [Table] [3]

| Table. Diagnostic criteria of streptococcal TSS |
|-----------------|-----------------|
| **A. Isolation of group A Streptococcus** | **B. Clinical signs of severity** |
| 1. From a sterile site | 1. Hypotension |
| 2. From a non-sterile site | 2. ≥ 2 of the followings: |
| | a. Renal impairment |
| | b. Coagulopathy |
| | c. Liver abnormalities |
| | d. Acute respiratory distress syndrome |
| | e. Extensive tissue necrosis, ie. necrotizing fasciitis |
| | f. Erythematous rash |
| **Definite Case = A1 + B (1+2)** | **Probable Case = A2 + B (1+2)** |


Patients with invasive streptococcal disease and TSS are typically very ill and, therefore, treatment should include empiric broad-spectrum antibiotics to cover potential pathogens [including coverage for both GAS and *S. aureus*] until GAS is confirmed. Other infections may produce signs and symptoms that can be confused with TSS and should be considered depending on the clinical context. These include leptospirosis, Rocky Mountain spotted fever and gram-negative sepsis. Prompt recognition and control of the infection source is of paramount importance [e.g. surgical debridement of necrotizing fasciitis]. De-escalation to penicillin G [3 to 4 million units i.v. every 4 h] plus clindamycin [600 to 900 mg i.v. every 6 to 8 h] for 10 to 14 days is recommended [4]. Clindamycin, a protein synthesis inhibitor, may provide additional benefit by suppressing the production of M proteins and superantigens. Further, clindamycin has been shown [in animal models of streptococcal myositis] to be more effective than penicillin due to the “Eagle effect” of reduced expression of penicillin binding proteins by GAS during the stationary growth phase [5]. The use of intravenous immunoglobulin (IVIG) has been described in small series, and a survival benefit with IVIG therapy was reported in a Canadian observational study [6]. A multicenter, randomized, double-blind, placebo-controlled trial demonstrated significant decrease in sepsis-related organ dysfunction and a trend toward improved survival with IVIG (mortality at 28 days was 3.6-fold higher in the placebo group), which was not statistically significant [7].

Ischemic optic neuropathy (ION), also known as stroke of the optic nerve, is a devastating condition that results from transient ischemia of the optic nerve. ION can affect one eye or both eyes simultaneously. Two different forms of ION exist: arteritic form [seen mostly in elderly patients with hypoperfusion of the optic nerve due to large vessel vasculitis, eg. temporal arteritis]; and non-arteritic ION (NAION) that can affect patients of any age and has been associated with transient hypotension presumably due to hypoperfusion of the paraoptic branches of the posterior ciliary artery. The incidence of NAION is 2.3–10.2 per 100 000 population in the United States [8]. Approximately 10% of non-arteritic ION occurs in individuals under the age of 45. The presence of atherosclerosis [e.g. due to diabetes mellitus], hypercoagulable state [e.g. anti-phospholipid antibody syndrome], or migraine increases the risk of NAION. Other risk factors include the traditional atherosclerosis risk factors such as smoking and hyperlipidemia. NAION presents with a rapidly progressive painless loss of vision [hours to days], usually described as dimness or blurring of the visual field.

Hypotension from any cause can result in NAION; this includes septic shock [as seen in our patient], hemorrhagic shock, or drug-induced hypotension [esp. beta blockers]. In fact, several non-antihypertensive medications have been described to cause NAION, such as interferon-alpha, amiodarone, and phosphodiesterase-5 inhibitors [9]. NAION remains stable in the majority of patients, although some
recovery of vision can be expected in up to 42% of patients [10]. The development of NAION may signify the presence of diffuse vasculopathy, and may be associated with increased risk of strokes and cardiovascular events [11]. Treatment of NAION is largely supportive and consists of prompt recognition and correction of shock. The role of other therapies [e.g. aspirin or corticosteroids] remains to be elucidated.

CONCLUSION
Streptococcal pharyngitis is an exceedingly rare cause of TSS. In our patient, it was most likely the source of a transient bacteremia seeding the knee joint, a process that probably was occurring as he was evaluated for pharyngitis. The rapidity of the development of shock is attributed to streptococcal exotoxins acting as superantigens, directly unleashing host inflammatory responses. GAS type M1 (our patient’s type) is commonly associated with severe shock in TSS. The profound hypotension was the likely cause of his ischemic optic neuropathy, which fortunately was reversible as he regained full vision. Early recognition and aggressive management that keep pace with the evolution of TSS are crucial to improve clinical outcome.

References

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Ten Years and Growing: Medical Marijuana in Rhode Island – Where Are We Now?

JAMES V. MCDONALD, MD, MPH; MIKE SIMOLI

BACKGROUND

The Edward O. Hawkins and Thomas C. Slater Medical Marijuana Act¹ (“Hawkins-Slater” – Rhode Island General Laws 21-28.6-1) became law in 2005. Regulations² were promulgated initially in July of 2006. The legislative findings³ incorporated in Hawkins-Slater assert that modern medical research recognizes beneficial uses for marijuana, including the treatment of pain, nausea and other debilitating conditions, noting that ten states (other than Rhode Island) had passed statutes approving the use of medical marijuana (“MM”).

Hawkins-Slater allows citizens with qualifying debilitating medical conditions (“QDMCs”) to grow, possess and use marijuana without fear of prosecution from state or federal law. “It is in the state’s interests of public safety, public welfare, and the integrity of the medical marijuana program to ensure that the possession and cultivation of marijuana for the sole purpose of medical use for alleviating symptoms caused by debilitating medical conditions is adequately regulated.”⁴ The law also allows individuals to become “primary caregivers” for citizens with QDMCs. The subsequent development of compassion centers (centers in which MM is grown commercially) was made possible by amending Hawkins-Slater in 2009.⁵ Three centers were subsequently opened in Rhode Island between spring, 2013⁶ and fall, 2014.⁷

At present, Rhode Island has ten years of experience in regulating MM.

USE OF MEDICAL MARIJUANA IN RHODE ISLAND

Currently, the Medical Marijuana Program lists 12,755 citizens¹⁰ with QDMCs. The number of certifications grew steadily between 2005 and 2013, then increased substantially. The number of primary caregivers also grew steadily between 2009 and 2012, then leveled off. (Figure 1) Three compassion centers are available to citizens with QDMCs.¹¹ At present, a patient may access any one – but only one – of the three centers (Table 1). Each patient is obligated to register with a center. Compassion centers offer marijuana-infused products in addition to the raw product.

A citizen with at least one QDMC¹² must be certified by a physician before applying to the Rhode Island Department of Health (RIDOH) to be approved to use MM. A physician’s certification indicates that “in the practitioner’s professional opinion, the potential benefits of the medical Marijuana would likely outweigh the health risks for a patient.”

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Table 1. Number of current citizens with a qualifying diagnosis or debilitating condition who have registered with a compassion center¹⁶

<table>
<thead>
<tr>
<th>Compassion Center</th>
<th>Number of Registrations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thomas Slater</td>
<td>7,025</td>
</tr>
<tr>
<td>Summit</td>
<td>3,058</td>
</tr>
<tr>
<td>Greenleaf</td>
<td>2,244</td>
</tr>
</tbody>
</table>
opinion, the potential benefits of the medical marijuana would likely outweigh the health risks for a patient. The process does not require medical review of the application or verification of a diagnosis.

Among all QDMCs, “chronic pain and persistent muscle spasms” is the most common (63%) reason for MM approval. [Table 2] Of note, the QDMC, “cancer or related treatment,” accounts for only 5.6% of all MM approvals. Among all patients approved to use MM, males outnumber females 2:1. [Table 3] Males are more likely than females to be certified on the basis of HIV positivity [5:1], AIDS [3.8:1], hepatitis-C [2.9:1], glaucoma [2.9:1], and pain [2.4:1]. Finally, more than half of all approved patients (53%) are below age 50. [Table 4]

**CERTIFYING PHYSICIANS**

Currently, only physicians licensed in Rhode Island, Massachusetts or Connecticut may certify that a citizen residing in Rhode Island has a QDMC. Currently, 69% are Rhode Island-licensed physicians and 31% are licensed in Massachusetts or Connecticut.
CONCLUDING THOUGHTS

Most physicians have not been trained in the pharmacology and clinical applications of MM, given its Schedule-1 designation. Of note, only five physicians account for 52% of Rhode Islanders approved for MM use. The diversity of the top five prescribers (internal medicine, surgery, anatomic pathology and obstetrics) is unexplained but raises questions. The vast majority of physicians in Rhode Island have not authorized MM for any of their patients, while another 13% have done so infrequently. What are the reasons for this? We have no data to provide answers.

References
4. Ibid [7]
6. The Thomas Slater Center: http://slatercenter.com/
8. Rhode Island General Laws § 21-28.6-3[9].
10. Rhode Island Department of Health MM program as of 12.31.2015
16. Rhode Island Department of Health MM Program as of 12.31.2015

Authors
James V. McDonald, MD, MPH, is Chief Administrative Officer, Board of Medical Licensure and Discipline, Rhode Island Department of Health.
Mike Simoli is Health Program Administrator, Center for Professional Licensing, Rhode Island Department of Health.
In the United States, the need for surveillance of suicide and suicide attempts is well recognized. In 2014, suicide was the second leading cause of death in the United States among young adults 15 to 24 years of age. During 1999-2014, the age-adjusted suicide rate in the United States increased by 50% for females aged 15 to 24, from 3.0 per 100,000 to 4.6 per 100,000. In contrast, the suicide rate for males aged 15 to 24 increased more slowly (16.8 per 100,000 in 1999 to 18.2 per 100,000 in 2014), but adolescent and young adult males are 4.0 to nearly 6.0 times more likely to die by suicide than their female counterparts. We characterize the burden of youth suicide injuries and deaths in Rhode Island (RI) using multiple data sources.

METHODS

The national and state Youth Risk Behavior Survey (YRBS) monitors self-reported health risk behaviors including violence-related behavior. Data for this study came from the 2003–2015 RI high school and 2009–2015 RI middle school YRBS. Attempted suicide was defined as the number of middle and high school students who, in the 12 months before the survey, actually attempted suicide one or more times.

Data from the 2014 RI Emergency Department (ED) Visit Data and RI Hospital Discharge Data (HDD) for 11 acute care hospitals were used to estimate attempted suicides and self-injuries among children and youth under age 25 using E950-E959 external cause of injury codes. Most payers require a single bill for patients seen in multiple units of the same hospital for a single stay. ED visits in this analysis did not include subsequent admissions to the same hospital.

The Rhode Island Violent Death Reporting System (RIVDRS) collects information from death certificates, medical examiner reports, and law enforcement sources. Suicide deaths came from the 2004 to 2014 RIVDRS using ICD-10-CM codes X60-X84, Y87.0. Characteristics of suicide attempts and suicide deaths, respectively, in young people under age 25 are shown in Tables 1 and 2. We performed all analyses using SAS version 9.4 [SAS Institute, Inc. Cary, NY].

RESULTS

Trend analysis over 12 years revealed that self-reported suicide attempts among RI middle school and high school students did not change significantly from 2003 to 2015, except for a striking change in 2013 (Figure 1).
schizophrenia (7%) occurring in smaller proportions [data not shown]. Over one-third of youth (36%) were in current mental health treatment. The most common precipitating events were mental health and substance abuse problems, relationship problems, recent crises, and school problems.

**DISCUSSION**

Our study found that the 388 ED visits for suicide attempts in youth under the age of 25 resulted in medical charges of almost $1.2 million dollars with average medical charges of approximately $3,000 per suicide attempt visit. The total charges for the 474 hospitalizations for suicide attempts in this age group were nearly $14.7 million dollars; the average medical charges were more than $30,000 per suicide attempt; and length of stay was 4,209 days [data not shown].

The reasons for suicide were complex. No single factor causes it. We found that children and youth who committed suicide were more likely to be male, white, living in suburban areas of the state, and having mental health problems. They also were more likely to have had current depression, intimate and non-intimate-partner relationship

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**Table 1. Characteristics of suicide attempts in young people under age 25**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Emergency Department Visits (N=388)</th>
<th>Hospital Discharges (N=474)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 18 years</td>
<td>195</td>
<td>50.3</td>
</tr>
<tr>
<td>18-24 years</td>
<td>193</td>
<td>49.7</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>139</td>
<td>35.8</td>
</tr>
<tr>
<td>Female</td>
<td>249</td>
<td>64.2</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>291</td>
<td>75.6</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>25</td>
<td>6.5</td>
</tr>
<tr>
<td>Hispanic</td>
<td>52</td>
<td>13.5</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>4.4</td>
</tr>
<tr>
<td><strong>City/Town of Residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban core cities</td>
<td>110</td>
<td>28.5</td>
</tr>
<tr>
<td>Suburban regions</td>
<td>202</td>
<td>52.3</td>
</tr>
<tr>
<td>Rural areas</td>
<td>59</td>
<td>15.3</td>
</tr>
<tr>
<td>Out of state</td>
<td>15</td>
<td>3.9</td>
</tr>
<tr>
<td><strong>Primary insurance</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>191</td>
<td>49.2</td>
</tr>
<tr>
<td>Medicaid</td>
<td>164</td>
<td>42.3</td>
</tr>
<tr>
<td>Self-pay</td>
<td>28</td>
<td>7.2</td>
</tr>
<tr>
<td>Medicare</td>
<td>5</td>
<td>1.3</td>
</tr>
<tr>
<td><strong>Patient Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discharged to home/self-care</td>
<td>258</td>
<td>66.6</td>
</tr>
<tr>
<td>Transferred to psychiatric unit or hospital</td>
<td>76</td>
<td>19.6</td>
</tr>
<tr>
<td>Other</td>
<td>54</td>
<td>13.9</td>
</tr>
</tbody>
</table>

1 Data source: 2014 Rhode Island Emergency Department (ED) Visit and Hospital Discharge Data (HDD). ED visits do not include those subsequent admissions to the same hospital.

2 Urban core cities: Central Falls, Pawtucket, Providence, and Woonsocket.

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**Table 2. Characteristics of suicide deaths in young people under age 25**

<table>
<thead>
<tr>
<th>Characteristics of Suicide Death</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group (mean: 19.7 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 18 years</td>
<td>30</td>
<td>23.6</td>
</tr>
<tr>
<td>18-24 years</td>
<td>97</td>
<td>76.4</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>102</td>
<td>80.3</td>
</tr>
<tr>
<td>Female</td>
<td>25</td>
<td>19.7</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>90</td>
<td>70.9</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>11</td>
<td>8.6</td>
</tr>
<tr>
<td>Hispanic</td>
<td>18</td>
<td>14.2</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>6.3</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
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<td></td>
</tr>
<tr>
<td>Middle school student</td>
<td>10</td>
<td>8.0</td>
</tr>
<tr>
<td>High school student</td>
<td>27</td>
<td>21.6</td>
</tr>
<tr>
<td>College student</td>
<td>28</td>
<td>22.4</td>
</tr>
<tr>
<td>Employed</td>
<td>41</td>
<td>32.8</td>
</tr>
<tr>
<td>Unemployed</td>
<td>9</td>
<td>7.2</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>8.0</td>
</tr>
<tr>
<td><strong>City/Town of Residence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urban core cities</td>
<td>38</td>
<td>30.2</td>
</tr>
<tr>
<td>Suburban regions</td>
<td>57</td>
<td>45.2</td>
</tr>
<tr>
<td>Rural areas</td>
<td>18</td>
<td>14.3</td>
</tr>
<tr>
<td>Out of state</td>
<td>13</td>
<td>10.3</td>
</tr>
<tr>
<td><strong>Injury Location</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>House, apartment</td>
<td>85</td>
<td>67.5</td>
</tr>
<tr>
<td>Natural area (e.g., field, river, beaches, woods)</td>
<td>16</td>
<td>12.7</td>
</tr>
<tr>
<td>Street/road, sidewalk, alley</td>
<td>&lt;5</td>
<td>2.4</td>
</tr>
<tr>
<td>Other*</td>
<td>22</td>
<td>17.4</td>
</tr>
<tr>
<td><strong>Injured at Victim Home</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>77</td>
<td>62.6</td>
</tr>
<tr>
<td>No</td>
<td>46</td>
<td>37.4</td>
</tr>
<tr>
<td><strong>Weapon Type</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Firearm</td>
<td>20</td>
<td>15.8</td>
</tr>
<tr>
<td>Hanging, strangulation, suffocation</td>
<td>78</td>
<td>61.4</td>
</tr>
<tr>
<td>Poisoning</td>
<td>9</td>
<td>7.1</td>
</tr>
<tr>
<td>Other</td>
<td>20</td>
<td>15.7</td>
</tr>
</tbody>
</table>

1 Data source: 2004–2014 Rhode Island Violent Death Reporting System; N=127

2 Urban core cities: Central Falls, Pawtucket, Providence, and Woonsocket.
problems, experienced a crisis in the preceding two weeks, left a suicide note, disclosed intent to commit suicide, and made prior suicide attempts. Approximately 47% of youth who died by suicide in RI were reported to have a depressed mood, while 36% were receiving mental health treatment. Mental health status could be underestimated. Our findings are consistent with the Dahlberg et al. study, which found that suicide in youth fundamentally reflects social and emotional problems. Of note is that 47% of suicide deaths among RI youth under age 25 were associated with current depression. Depression, which is a serious problem for adolescents, is the most significant risk factor for teen suicide.7

Data from Rhode Island’s suicide event surveillance system drew attention to the prevalence of youth suicide attempts and deaths and the magnitude of the problem. National suicide prevention efforts have focused on school education programs, crisis center hotlines, and screening programs to identify at-risk adolescents. RI developed the Suicide Prevention Initiative [SPI] to address the link between suicide and depression, two treatable mental health conditions that, once recognized, can be treated.8 SPI is a new partnership between the RI Department of Health, Rhode Island Student Assistance Services (RISAS), and Bradley Hospital’s Access Center and Kids’Link RI hotline for children in emotional crisis [East Providence, RI]. It is funded by a five-year grant from the Substance Abuse and Mental Health Administration [2014–2019]. SPI is a direct referral system that links school crisis team members with Kids’Link RI emergency service clinicians. Once parental consent is obtained, Kids’Link clinicians provide emergency mental health assessments for elementary, middle and high school youth who are experiencing a mental health crisis or suicidal ideation. Clinicians are available 24 hours a day, seven days a week to help families find the appropriate next step for managing the child’s crisis. SPI is being implemented and evaluated in school districts throughout RI to ensure that all public school students who express suicidal ideation or engage in non-suicidal, self-injurious behavior receive timely [within 24 to 48 hours] access to mental health services, thus avoiding unnecessary and costly emergency department visits.

There are several limitations to the data reported in this study. Data obtained from medical examiner reports could only determine the mental health status of the victims through medical records or the presence of certain prescription drugs, but not all persons with a mental illness seek treatment. Data on a person’s mental health status from interviews with victims’ family members, relatives, friends, or other informants, may be incomplete and inaccurate because of recall bias. Information on mental health history was unknown in some RIVDRS cases.

Despite these limitations, RI’s surveillance system for suicide attempts and deaths are extremely useful for describing the characteristics and patterns of suicidal behavior among RI youth under age 25. Ongoing surveillance of suicide-related events across the suicide-related spectrum [e.g., thoughts, attempts, deaths] in population subgroups [e.g., sex, age, and racial/ethnic groups, geographic regions of the state] provide a much needed foundation for establishing state priorities to reduce and prevent youth suicides and for developing successful prevention efforts.10

### Table 3. Suicide death toxicology tests and circumstances in young people under age 25

<table>
<thead>
<tr>
<th>Toxicology Test and Circumstance</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tested</td>
<td>126</td>
<td>99.2</td>
</tr>
<tr>
<td>Toxicology test positive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>29</td>
<td>23.0</td>
</tr>
<tr>
<td>Marijuana</td>
<td>27</td>
<td>21.4</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>27</td>
<td>21.4</td>
</tr>
<tr>
<td>Opiates</td>
<td>8</td>
<td>6.4</td>
</tr>
<tr>
<td>Mental health/substance abuse circumstance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current depressed mood</td>
<td>60</td>
<td>47.2</td>
</tr>
<tr>
<td>Current diagnosed mental health problem</td>
<td>57</td>
<td>44.9</td>
</tr>
<tr>
<td>Depression/Dysthymia</td>
<td>42</td>
<td>--</td>
</tr>
<tr>
<td>Attention deficit or hyperactivity disorder</td>
<td>11</td>
<td>--</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>9</td>
<td>--</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>6</td>
<td>--</td>
</tr>
<tr>
<td>Other</td>
<td>17</td>
<td>--</td>
</tr>
<tr>
<td>Current mental health treatment</td>
<td>46</td>
<td>36.2</td>
</tr>
<tr>
<td>Other substance abuse problem</td>
<td>20</td>
<td>15.8</td>
</tr>
<tr>
<td>Alcohol problem</td>
<td>9</td>
<td>7.1</td>
</tr>
<tr>
<td>Interpersonal circumstance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intimate partner problem</td>
<td>40</td>
<td>31.5</td>
</tr>
<tr>
<td>Other relationship problem</td>
<td>28</td>
<td>22.1</td>
</tr>
<tr>
<td>Family relationship</td>
<td>20</td>
<td>15.8</td>
</tr>
<tr>
<td>An argument or conflict led to the victim’s death</td>
<td>14</td>
<td>11.0</td>
</tr>
<tr>
<td>Life stressor circumstance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crisis in past or impending two weeks</td>
<td>37</td>
<td>29.1</td>
</tr>
<tr>
<td>School problem</td>
<td>13</td>
<td>10.2</td>
</tr>
<tr>
<td>Job problem</td>
<td>9</td>
<td>7.1</td>
</tr>
<tr>
<td>Civil legal (non-criminal) problem</td>
<td>6</td>
<td>4.7</td>
</tr>
<tr>
<td>Recent criminal legal problem</td>
<td>6</td>
<td>4.7</td>
</tr>
<tr>
<td>Financial problem</td>
<td>5</td>
<td>3.9</td>
</tr>
<tr>
<td>Suicide event circumstance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left a suicide note</td>
<td>41</td>
<td>32.3</td>
</tr>
<tr>
<td>Disclosed intent to commit suicide</td>
<td>30</td>
<td>23.6</td>
</tr>
<tr>
<td>History of suicide attempt(s)</td>
<td>28</td>
<td>22.1</td>
</tr>
<tr>
<td>Suicide thought history</td>
<td>8</td>
<td>6.3</td>
</tr>
</tbody>
</table>

2 Percentages may exceed 100% because test results can be positive for alcohol or multi-drugs.
3 One victim can have two or three current mental health diagnoses.
Acknowledgments

This brief was funded by a Centers for Disease Control and Prevention (CDC) grant (1U17CE002615-01 Revised) awarded to the Rhode Island Department of Health. We would like to express our special thanks to data abstractors Karen Foss and Shannon Young, who spent hours compiling the data and constructing sound narratives to make RIVDRS one of the best. We thank Kathy Taylor who provided the 2014 emergency department and hospital discharge data. We also thank Tara Cooper for her contribution as the YRBS coordinator.

References


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Disclosure

The authors have no financial interests to disclose.

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yongwen.jiang@health.ri.gov
Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

<table>
<thead>
<tr>
<th>VITAL EVENTS</th>
<th>JUNE 2016</th>
<th>12 MONTHS ENDING WITH JUNE 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Number</td>
<td>Rates</td>
</tr>
<tr>
<td>Live Births</td>
<td>1,006</td>
<td>11,662</td>
</tr>
<tr>
<td>Deaths</td>
<td>737</td>
<td>10,065</td>
</tr>
<tr>
<td>Infant Deaths</td>
<td>2</td>
<td>57</td>
</tr>
<tr>
<td>Neonatal Deaths</td>
<td>1</td>
<td>42</td>
</tr>
<tr>
<td>Marriages</td>
<td>840</td>
<td>6,828</td>
</tr>
<tr>
<td>Divorces</td>
<td>284</td>
<td>3,143</td>
</tr>
<tr>
<td>Induced Terminations</td>
<td>167</td>
<td>2,308</td>
</tr>
<tr>
<td>Spontaneous Fetal Deaths</td>
<td>40</td>
<td>566</td>
</tr>
<tr>
<td>Under 20 weeks gestation</td>
<td>34</td>
<td>501</td>
</tr>
<tr>
<td>20+ weeks gestation</td>
<td>6</td>
<td>65</td>
</tr>
</tbody>
</table>

* Rates per 1,000 estimated population
# Rates per 1,000 live births

<table>
<thead>
<tr>
<th>Underlying Cause of Death Category</th>
<th>DECEMBER 2015</th>
<th>12 MONTHS ENDING WITH DECEMBER 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (a)</td>
<td>Number (a)</td>
<td>Rates (b)</td>
</tr>
<tr>
<td>Diseases of the Heart</td>
<td>216</td>
<td>2,407</td>
</tr>
<tr>
<td>Malignant Neoplasms</td>
<td>162</td>
<td>2,267</td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>36</td>
<td>434</td>
</tr>
<tr>
<td>Injuries (Accident/Suicide/Homicide)</td>
<td>61</td>
<td>842</td>
</tr>
<tr>
<td>COPD</td>
<td>38</td>
<td>517</td>
</tr>
</tbody>
</table>

(a) Cause of death statistics were derived from the underlying cause of death reported by physicians on death certificates.
(b) Rates per 100,000 estimated population of 1,056,298 (www.census.gov)
(c) Years of Potential Life Lost (YPLL).

NOTE: Totals represent vital events, which occurred in Rhode Island for the reporting periods listed above. Monthly provisional totals should be analyzed with caution because the numbers may be small and subject to seasonal variation.
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November 3, Thursday
Meeting with Rhode Island Bike Coalition
AMPAC check presentation to Congressman Cicilline, Michael Silver, MD, Chair RIMPAC
Governor’s Health Care Work Force Transformation/Mental Health

November 7, Monday
Meeting with Secretary of the Executive Office of Health and Human Services
Meeting with Blue Cross Blue Shield of RI regarding recruitment video
Meeting of Weight and Wellness Planning Committee
RIMS Board of Directors Meeting

November 8, Tuesday
Election Day

November 9, Wednesday
Board of Medical Licensure and Discipline
Governor’s Opioid Taskforce
Meeting with OHIC regarding legislation and Modifier 25
Blue Cross Provider Symposium: “New Frontiers in Reimbursement”

November 10, Thursday
Meeting with Purdue Pharma regarding CME event
Meeting with Chair of Senate Health and Human Services Committee regarding legislation

November 11–15, Friday–Tuesday
AMA Interim Meeting, Orlando, Florida, Sarah Fessler, MD, President; Peter Hollmann, MD, AMA Delegate; Alyn Adrain, MD, AMA Delegate; and staff attending

November 16, Wednesday
Primary Care Physician Advisory Committee
Meeting of opioid treatment providers
Workers Compensation Advisory Committee

November 17, Thursday
Senate Health and Human Services Committee hearing on mental health

November 18, Friday
Meeting with Ailis Clyne, MD, MPH, Medical Director, Division of Community Health and Equity, RI Dept. of Health; regarding Weight and Wellness Summit

November 21, Monday
Primary Care Physician Advisory Committee

November 22, Tuesday
AMA Advocacy Resource Center conference call regarding E-Prior Authorization
SIMS Steering Committee, Peter Hollmann, MD
Physician Advisory Committee

November 23, Wednesday
Interdisciplinary Pain Management at Department of Health

November 28, Monday
Alpert Medical School Citizen Physician Group Meeting at RIMS; Sen. Chris Ottiano, MD, and Staff

RIMS staff members Steve DeToy, Sarah Stevens, and Newell Warde volunteer for RIMS President-Elect Bradley J. Collins, MD, on Election Day.
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This event is made possible through an educational grant from the Coverys Community Healthcare Foundation.
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Care New England was founded in 1996 and is the parent organization of Butler, Kent, Memorial and Women & Infants hospitals, the VNA of Care New England, The Providence Center, CNE Wellness Center and Integra, a certified Accountable Care Organization. Care New England includes 970 licensed beds and 216 infant bassinets. Through Butler, Memorial and Women & Infants, Care New England has a teaching and research affiliation with The Warren Alpert Medical School of Brown University. Kent is a teaching affiliate of the University of New England College of Osteopathic Medicine.

Doctor's Choice provides no cost Medicare consultations. Doctor's Choice was founded by Dr. John Luo, a graduate of the Alpert Medical School at Brown University to provide patient education and guidance when it comes to choosing a Medicare Supplemental, Advantage, or Part D prescription plan. Doctor's Choice works with individuals in RI, MA, as well as CT and helps compare across a wide variety of Medicare plans including Blue Cross, United Health, Humana, and Harvard Pilgrim.

Neighborhood Health Plan of Rhode Island is a non-profit HMO founded in 1993 in partnership with Rhode Island's Community Health Centers. Serving over 185,000 members, Neighborhood has doubled in membership, revenue and staff since November 2013. In January 2014, Neighborhood extended its service, benefits and value through the HealthSource RI health insurance exchange, serving 49% the RI exchange market. Neighborhood has been rated by National Committee for Quality Assurance (NCQA) as one of the Top 10 Medicaid health plans in America, every year since ratings began twelve years ago.

RIPCPC is an independent practice association (IPA) of primary care physicians located throughout the state of Rhode Island. The IPA, originally formed in 1994, represent 150 physicians from Family Practice, Internal Medicine and Pediatrics. RIPCPC also has an affiliation with over 200 specialty-care member physicians. Our PCP's act as primary care providers for over 340,000 patients throughout the state of Rhode Island. The IPA was formed to provide a venue for the smaller independent practices to work together with the ultimate goal of improving quality of care for our patients.

The Rhode Island Medical Society continues to drive forward into the future with the implementation of various new programs. As such, RIMS is expanded its Affinity Program to allow for more of our colleagues in healthcare and related business to work with our membership. RIMS thanks these participants for their support of our membership.

Contact Megan Turcotte for more information: 401-331-3207 or mturcotte@rimed.org
RIMS gratefully acknowledges the practices who participate in our discounted Group Membership Program.
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Body Worlds Exhibit: Anatomy Up Close & Personal

MARY KORR
RIMJ MANAGING EDITOR

PROVIDENCE – The recent Body Worlds Vital exhibition at the museum gallery in the Rhode Island Convention Center offered an anatomic, athletic and artistic view of the human body.

The approximately 200 specimens on display were preserved through a process Dr. Gunther von Hagens developed in Germany in 1977 at the Anatomical Institute of Heidelberg University he termed Plastination. Since that time, he has refined the process; his first whole-body plastinate was created in 1992.

The Plastination method extracts bodily fluids and fat from specimens, replaces them with acetones, which in a second step is replaced by polymers. The body is then positioned, with the entire anatomical structure properly aligned and secured with wires, needles, clamps, and foam blocks. In the final step, the specimen is hardened. Depending on the polymer used, this is done with gas, light, or heat.

The Providence exhibit included whole body figures, as well as individual organs, blood vessel configurations, and transparent longitudinal and cross-sectional body slices, allowing viewers to observe the anatomy and working of the human body, and the effects of disease on it, often by comparing healthy and diseased organs. Two in the exhibit showed black lungs illustrating the effects of smoking. Long-term outcomes of disorders, and substance abuse are illustrated in the same way, as are the mechanics of artificial hip and knee joints.

All of the specimens in Body World exhibits, which have been seen by millions around the world, are from individuals who have willed their bodies to the donation program managed by the Institute for Plastination in Heidelberg, Germany.

Donors agree that their bodies will be permanently preserved and used in displays for the education of future generations.

The identity, age at death, and cause of death of the donors are not revealed. A few of the plastinates in the exhibitions originate in old anatomical collections, which is particularly true of the embryos shown.

The Institute for Plastination has more than 16,000 donors on its roster, and more than 1,400 of them are Americans.

Dr. von Hagens, who announced he suffers from Parkinson’s disease, has signed up for his own program and will have his body plastinated so that people can learn about PD.

Up-to-date information on the traveling exhibitions is available at www.bodyworlds.com.

The Soccer Player
Shown here and on the front cover, this plastinate shows all the muscles just below the skin. The skeletal muscles all overlap intricately. Photo © Gunther von Hagens’ BODY WORLDS, Institute for Plastination, Heidelberg, Germany, www.bodyworlds.com. All rights reserved.

The Orthopedic Body
(Below left) This plastinate is posed as a dancer. It is fitted with artificial joints at the knee, hip, and elbow. The jawbone has also been partly replaced. Some of the instruments are surgical. Others are for orthopedics.

(Below right) Plastinate of a man holding his skin.
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Alpert Foundation awards Brown medical school $27M
Funds will endow MD/PhD program; create Translational Science professorship

PROVIDENCE — A new $27 million gift to Brown from The Warren Alpert Foundation will establish an endowment for Brown’s program for training MD/PhD students pursuing careers as “physician-scientists,” more than tripling funding for the program, and will create the first endowed professorship in the Brown Institute for Translational Science.

Of the total gift, $22 million will establish the endowed Warren Alpert Physician-Scientist MD/PhD and Advanced Training Program, offering more students the opportunity to pursue these joint degrees with tuition assistance and research stipends.

The gift will also bolster efforts to bring researchers from different fields together to decipher disease and improve population health, one of the seven integrative scholarship themes outlined in the University’s Building on Distinction strategic plan.

DR. JACK A. ELIAS, Brown’s dean of medicine and biological sciences and the Frank L. Day Professor of Biology, said that a thriving MD/PhD program is an essential component for medical schools focused on translational science and that the foundation’s gift will advance the University’s vision to become a world-class center of innovation in biology and medicine.

“MD/PhD physician researchers see patients in the clinic, understand the challenges of the diseases they study and transfer those insights to work in their labs,” Elias said.

“These scholars are integral in the research continuum and a critical ingredient for any school to truly excel in translational research.”

DR. ALLAN TUNKEL, associate dean for medical education, said that tuition assistance is particularly beneficial for MD/PhD students and will allow Brown to attract exceptional students who have the passion for combining research with clinical medicine. For years, Brown students have wanted more opportunities to engage in this extraordinary level of scholarship, he said.

Bolstering translational science
The gift’s additional $5 million will establish the Warren Alpert Professorship as the first endowed professorship in the Brown Institute for Translational Science (BITS). Established in fall 2015, BITS organizes researchers into integrated teams with a full continuum of expertise – from basic science to medicine to population health and policy – to make breakthroughs on specific diseases and other pressing medical challenges in society.

The new professorship will enable the institute to recruit and support a new faculty member with in-demand expertise integral in translating scientific discoveries into applicable solutions for health issues, a key factor in the institute’s plans to assemble fully integrated teams that can attack medical problems from multiple directions.

AMA Adopts New Policies to Support Medical Student and Resident Physician Wellness and Mental Health

ORLANDO – The American Medical Association (AMA) adopted new policy recently aimed at ensuring medical students and resident and fellow physicians have timely and confidential access to the medical and mental health services they need during their medical training. The new policies will help physicians-in-training maintain their personal health and well-being and reduce burnout so they can provide the highest quality patient care.

“Many physicians-in-training do not seek out treatment for physical, mental health or addiction issues because they are concerned about confidentiality, the possible negative impact that receiving treatment could have on their future career in medicine, or burdening colleagues with extra work,” said AMA Board Member and medical student Omar Z. Maniya. “With a high number of medical students and residents experiencing depression, burnout and suicide, and too many physicians overlooking their own health needs, we must do everything we can to reduce the barriers and stigmas that keep them from receiving care.”

To help address concerns about confidentiality, the new policy specifically calls on state medical boards to refrain from asking applicants about past history of mental health diagnosis or treatment, and only focus on current impairment by mental illness or addiction, and to accept “safe haven” non-reporting, which would allow physicians-in-training who are receiving mental health treatment to apply for licensure without having to disclose it.

The new policy also encourages medical schools to create mental health awareness and suicide prevention screening programs that would be available for all medical students at their discretion. The policy asks that these programs offer students anonymity, confidentiality, and protection from administrative action, and provide proactive intervention for any student identified as at-risk by mental health professionals. These policies build on the AMA’s strategic work over the past several years to reduce physician burnout and create the medical school of the future. The AMA is committed to ensuring a healthier practice environment for physicians and closing the gaps that exist in medical education to improve the health of the nation.
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Bradley Hasbro Children’s Research Center awarded $3.3M NIH grant to study effects of trauma on teens and value of social media in recovery

PROVIDENCE – NICOLE NUGENT, PhD, a pediatric psychologist from the Bradley Hasbro Children’s Research Center, is leading a new study to better understand the social and biological factors that may promote resilience in teens after a traumatic event. The $3.3-million, 5-year National Institutes of Mental Health [NIMH] study will be used to develop interventions to help adolescents better recover from trauma.

“Trauma-exposed adolescents are at risk for a host of negative outcomes, including symptoms of posttraumatic stress disorder, anxiety, depression and substance abuse disorders,” said Nugent. “Although researchers have very generally shown that friends and family, as well as an adolescent’s own biological responses, are important for adjustment after trauma, there is much we still don’t know about the exact timing and types of help that friends and family can provide. In particular, we know very little about how the use of social media may affect a teen’s adjustment after trauma.”

The study will evaluate 200 trauma-exposed adolescents between the ages of 13 and 17 who have been medically evaluated in the Hasbro Children’s Hospital emergency department after a traumatic injury, such as a physical assault or a serious vehicular accident. Participants will be asked to wear a watch and carry a phone to track their heart rate, skin conductance and acoustic environment, as well as participate in clinical interviews and stress testing for a follow-up period.

Nugent’s hope is that the study findings will help make clearer recommendations to families about how they can best support their adolescent after trauma, including clearer recommendations about the effects of social media use for adolescents during the first few weeks following trauma.

“This research is the first of its kind that allows us to really understand how social supports play out in the real world over the course of the critical first few weeks after trauma,” said Nugent. “These findings will help us to also develop new interventions that could be provided for families, possibly including interventions that incorporate ways to best harness social media use.”

This research is supported by the National Institutes of Mental Health under Award Number R01MH108641. Nurget’s principal affiliation is the Bradley Hasbro Children’s Research Center, a division of the Lifespan health system in Rhode Island. She is also an associate professor (research) at The Warren Alpert Medical School of Brown University, departments of psychiatry and human behavior and pediatrics.

AMA Launches Textbook to Train Physicians on ‘Third Science’

CHICAGO – As part of its ongoing effort to develop bold, innovative ways to improve physician training, the American Medical Association (AMA) recently launched a new health systems textbook. The AMA collaborated with its 32-school Consortium to identify the innovations needed to create the medical school of the future. “Health Systems Science” emerged as the third pillar of medical education that should be integrated with the two existing pillars: basic and clinical sciences.

JEFFREY BORKAN, MD, PhD, assistant dean for the Primary Care-Population Medicine Program Planning at the Alpert Medical School, contributed to the textbook, which focuses on value in health care, patient safety, quality improvement, teamwork and team science, leadership, clinical informatics, population health, socio-ecological determinants of health, health care policy and health care economics.

Many schools within the Consortium have already begun implementing Health Systems Science into their curricula and will soon use the textbook with their students, including Brown, which also received a $1 million AMA grant to support its curriculum transformation, created its Primary Care-Population Medicine program—awarding graduates both a Doctor of Medicine and a Master of Science in Population Medicine. The first-in-the-nation program is designed to develop physicians who, with training focused on population health, can be future leaders in community-based primary care at the local, state or national level.

Topics in the textbook include:

• Patient safety
• Quality improvement
• Teamwork and team science
• Leadership
• Clinical informatics
• Population health
• Socio-ecological determinants of health
• Health care policy and economics

“Health Systems Science,” published by Elsevier, can be preordered from the AMA Store and Elsevier, as well as from Amazon and other online booksellers. The textbook retails for $59.99. AMA members may order it from the AMA Store for $54.99. Individual chapters will also be available from Elsevier for $5.99 each.
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Women & Infants Files Letter of Intent for Renovation of Labor and Delivery Suite

PROVIDENCE – Women & Infants Hospital of Rhode Island has filed a letter of intent [LOI] with the Rhode Island Department of Health for its proposal, “Women & Infants Hospital Labor & Delivery Renovation.” This LOI is the first step in the hospital’s plan to file a certificate of need [CON] application in January 2017.

As one of the largest stand-alone obstetrical services in the country, Women & Infants delivered more than 8,800 babies last year. Since the current space was designed in 1986, there have been dramatic changes in the hospital’s patient population, care models and the introduction of new technologies. Women & Infants has seen a sizable increase in patients with significant chronic illness who require specialized monitoring and care; has moved to an electronic medical records system; and has instituted a team-based model of care that includes patients and families in all aspects of care.

“As a specialty hospital with a unique focus, Women & Infants is a well-cherished jewel, providing incomparable care to the women and newborns of our region. But our physical environment in labor and delivery no longer provides the optimal support for today’s modern birth approach,” said MARK R. MARCANTANO, president and chief operating officer of Women & Infants Hospital. “It’s time for our physical environment in labor and delivery to match the incredible level of clinical care provided here.”

Women & Infants’ Labor and Delivery Suite is comprised of 19 private labor/delivery/recovery rooms, three dedicated Cesarean birth rooms and a recovery area, and an Alternative Birthing Center that offers a high-touch, home-like, midwife-led birthing experience for low-risk births. This project will consist of renovating all 20 labor rooms and increasing the room size from 220 square feet to the current guidelines of 400 square feet with a private bathroom and shower in each room.

“The project design will be based around a universal room that exceeds the needs for all levels of patient and family centered care. The renovation will integrate the newest technologies and include upgrades to the electrical, HVAC, plumbing and medical gasses systems.

The renovation, with a projected cost of approximately $18.6 million, is scheduled to be completed in October 2018 will be done in phases over 14 to 16 months in order to minimize any disruption to existing service.

“Having a baby is a wonderful experience for a family,” said JAMES A. O’BRIEN, MD, director of inpatient obstetrics and an assistant professor of obstetrics and gynecology at The Warren Alpert Medical School of Brown University. “We want to provide the highest level of complex care when necessary, but also provide a warm, personal and engaging experience, with hidden technology that is only used as needed.”

Stoico/FIRSTFED Charitable Foundation donates $1.1M for maternity care at St. Luke’s Hospital in New Bedford

NEW BEDFORD – Southcoast Health announced recently that the Robert F. Stoico/FIRSTFED Charitable Foundation has donated $1.1 million to the Campaign for Southcoast Health – a $25 million capital fundraising campaign which is the largest in the not-for-profit healthcare system’s history. The Maternity Center at St. Luke’s Hospital in New Bedford will receive $1 million, while the additional $100,000 will go towards the care of drug-addicted newborns.

“Healthcare is extremely important to me and my foundation,” said Bob Stoico, who began the foundation after retiring as chairman, president and CEO of FIRSTFED America Bancorp Inc. “By supporting excellent maternity care at St. Luke’s, we are helping to ensure the health and well-being of families. That is a vital service for the community.”

Southcoast Health is the only provider of maternity services at all three sites offer a family-centered approach that provides the right combination of compassionate care and the latest technology.

“We are incredibly grateful to the Stoico/FIRSTFED Charitable Foundation for this extremely generous donation, which benefits moms, newborns and families,” said KEITH A. HOVAN, President & CEO of Southcoast Health. “As a not-for-profit healthcare system, we rely on the generosity of so many within our community to support vital programs and services. This substantial contribution has helped us to completely renovate our maternity department at St. Luke’s, where families in greater New Bedford can now celebrate the birth of a child in a brand new, state-of-the-art unit that offers privacy and comfort.”

The Campaign for Southcoast Health is currently raising funds to support major capital initiatives across Southcoast Health’s three acute-care hospitals – St. Luke’s, Charlton Memorial in Fall River and Tobey in Wareham.
Drs. Gruppuso, Adashi question ‘residency placement fever’

PROVIDENCE — The highly successful process of matching medical graduates to residencies has nevertheless become so frenzied that the authors of a new article in *Academic Medicine* explicitly question the rationality of the system. It’s driving up costs for students and severely disrupting the fourth year of medical school, they say.

“There’s been this inexorable intensification of the residency selection process such that it’s basically taken over the fourth year of medical school,” said DR. PHIL GRUPPUSO, a professor of pediatrics in the Alpert Medical School and a former associate dean for medical education. “It so dominates student time and energy during the fourth year that it’s become very difficult to do any curriculum planning.”

The statistics he uncovered with co-author DR. ELI ADASHI, former dean of medicine and biologic sciences at Brown, show that by 2005, students across the country were applying on average to 30.3 programs. In 2015 the number reached 45.7. For specialties deemed highly competitive, the numbers go even higher: The average student hoping to be an orthopedic surgeon, for example, applied to 73 of the 163 potential programs.

The surge of residency program applications appears to derive from a perception among students that it’s necessary to ensure placement in a top program. Indeed, among all applicants to residency programs, the number of offers per applicant fell to 0.78 in 2015 from 0.96 in 1976.

Among MD graduates in the U.S., the number of offers per applicant has actually increased to 1.51 in 2015 from 1.37 in 1976.

Disruptive, costly and maybe unfair

After students file their [many, many] applications electronically, programs invite their preferred students for interviews. Here Gruppuso and Adashi could find no national data, but a survey of fourth-year students at the Alpert Medical School suggests that the number of interviews has scaled up with the number of applications. That means that students are on the road for substantial chunks of time throughout their fourth year of school. Interviews among programs and disciplines are not coordinated, making it hard for faculty members to plan a curriculum in which students can fully participate.

Meanwhile, Gruppuso and Adashi wrote, the financial burden of traveling to many interviews around the country may significantly disadvantage students of low socio-economic status, though that’s never been formally studied.

Data, solutions needed

More than anything, Gruppuso and Adashi call for more data so that medical educators can either prove or disprove the “more is better” hypothesis that students appear to have accepted as a new normal.

Gruppuso and Adashi also propose a few steps that medical education organizations such as the National Residency Matching Program, the Association of American of Medical Colleges and the American Medical Association could take to treat what they call the “Residency Placement Fever.”

- Coordinate interview timing: If student interviews could be consolidated into a predictable, cohesive season, educators could plan a meaningfully educational curriculum for the rest of the fourth year.
- Reduce or cap the number of interviews: If students could only take on a maximum of 10 interviews, they might be more thoughtful and selective about where they sent applications.
- A “screen and schedule” system: If residency programs employed online screening interviews before inviting applications in person, that could reduce unnecessary time and travel for students who don’t become finalists.

Adashi and Gruppuso readily acknowledge these particular ideas might not take hold, but they argue it’s certainly time for an examination of whether the current state of residency applications makes sense.

IN THE NEWS

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Appointments

Demetra C. Ouellette named President of Roger Williams Medical Center

PROVIDENCE — DEMETRA C. OUELLETTE has been named President of Roger Williams Medical Center following an extensive search. She brings a proven track record as a leader focused on improving quality, patient satisfaction and safety. Ouellette joins Roger Williams from Prime Healthcare Services, where she served as Chief Operating Officer/Administrator for Landmark Medical Center, Rehabilitation Hospital of RI, and Landmark Physician Outpatient Services.

Previously, she served as Corporate Vice President, Business Development with Select Medical Corporation in Pennsylvania and was President and CEO of Ouellette and Associates Healthcare Interim Management. Her previous employers include The Studer Group and Tenet Healthcare Corporation.

A graduate of Tufts University, Ouellette holds an MBA from Northeastern University.

Lawrence T. Saulnier, RN, BSN, Joins Visiting Nurse of Hope-Health as Director of Nursing

LINCOLN — LAWRENCE T. SAULNIER, RN, BSN, has joined the Visiting Nurse of HopeHealth agency as director of nursing. In his new role, Saulnier will be responsible for strategic leadership and program development and implementation. He will also oversee overall administration of nursing services in accordance with patients’ needs, government regulations and projected industry changes.

Saulnier brings more than ten years’ of clinical expertise and leadership experience to his new position. Most recently, he was a clinical nurse manager at the Visiting Nurse Association of Care New England. There, he was responsible for supervising the clinical staff and admission team, helping to assist with their intake process. He also championed numerous clinical initiatives designed to improve performance. Prior to this role, he worked at South County Hospital as an RN, where he provided nursing care to patients in a variety of in-patient settings.

He holds his bachelor of science in nursing degree from Dominican College and a bachelor of science-health and human services-police science from Empire State College.

Phyllis A. Dennery, MD, named president-elect of Society for Redox Biology and Medicine

PROVIDENCE — PHYLLIS A. DENNERY, MD, pediatrician-in-chief at Hasbro Children’s Hospital, has been voted president-elect of the Society for Redox Biology and Medicine (SRBM). Dennery was installed as president-elect at SRBM’s annual meeting scheduled from Nov. 16–19. Her two-year term as president will begin in 2018.

Established in 1987, the SRBM is a professional organization of scientists and clinicians investigating redox biology, which is the study of free radicals and reactive oxygen as they relate to human diseases and potential therapeutic interventions.

Dennery has been a member of the society since 1990 and has served on various committees and on the society’s council. She served as associate editor of the society publication Free Radicals in Biology and Medicine from 2003 until March of this year.

Not only will Dennery be the first African-American to serve as SRBM president, she will also be the first physician president of the society.

“I hope that in my role as president, I can use my background as a physician to bring clinical context to some of the diseases we research as a society,” said Dennery. “I would like to expand our society’s scope to consider everything from basic science to clinical medicine. We need to examine every aspect of free radicals and delve into how biology relates to patients and their diagnoses.”

Dennery hopes that an expanded view of the field of redox biology will lead to partnerships with other groups and societies, as well as physician groups.

Dennery, a Howard University College of Medicine graduate, joined Hasbro Children’s Hospital in April 2015, bringing more than 25 years of experience in pediatric care, teaching and research. In addition to her role as pediatrician-in-chief and medical director, she is also the Sylvia Kay Hassenfeld Chair of Pediatrics at the Warren Alpert School of Medicine of Brown University and a professor of molecular biology, cell biology and biochemistry at Brown University.

At Hasbro Children’s Hospital, Dennery oversees all pediatric clinical programs, such as centers and clinics for pediatric imaging, hematology/oncology, asthma and allergies, neurodevelopment and cardiology. Dennery’s research on lung problems and other medical conditions among newborns has been funded by the National Institutes of Health for 24 consecutive years.

Dennery is a member of the National Academy of Medicine (formerly Institute of Medicine), the Society for Pediatric Research, and the American Pediatric Society, among many others and also serves as an associate editor of the journal Pediatrics. She has received numerous awards during her career, including the 2014 Marion Spencer Fay Award, Best Doctors in America, and the Alfred Stengel Health System Champion Award. Dennery was recently elected to the Association of American Physicians, one of the highest honors in academic medicine.
**Appointment**

Dr. Eden Cardozo joins W&I, will oversee Fertility Preservation Program

PROVIDENCE – EDEN CARDozo, MD, of Boston, has recently joined the Division of Reproductive Endocrinology and Infertility in the Department of Obstetrics and Gynecology at Women & Infants Hospital. Dr. Cardozo is also an assistant professor at The Warren Alpert Medical School.

Her areas of research and clinical interest include fertility preservation and the impact of obesity on reproductive outcomes.

“I am very proud to join the team at Women & Infants’ Fertility Center and, in particular, the Fertility Preservation Program. This wonderful program allows patients to use cutting edge techniques to preserve their fertility for the future,” said Dr. Cardozo. “The road to building a family – now or in the future – can be complicated and overwhelming. My goal is for patients to feel comfortable engaging in open and honest conversation with me, which I feel is crucial in helping my patients to achieve their goals.”

A graduate of Yale University, Dr. Cardozo earned her medical degree at the University of Michigan Medical School. She completed a residency in obstetrics and gynecology at the Feinberg School of Medicine at Northwestern University, and a fellowship in reproductive endocrinology and infertility at Massachusetts General Hospital, Harvard Medical School. She is a member of the American Congress of Obstetricians and Gynecologists, the American Society for Reproductive Medicine, the New England Fertility Society, and the Society for Reproductive Investigation.

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**Recognition**

Roger Williams Cancer Center recognized at American Cancer Society’s 2016 Rhode Island Research Breakfast

PROVIDENCE – The Cancer Center at Roger Williams Medical Center was recognized at the American Cancer Society’s 3rd annual Rhode Island Research Breakfast for receiving the Commission on Cancer’s “Outstanding Achievement Award.”

The event, which took place on October 14, is hosted by the American Cancer Society’s Cancer Action Network and brings together leaders, medical professionals and cancer survivors from across the state to address the need for increased funding of cancer research. DR. N. JOSEPH ESPAT, Chairman of Surgery and Director of the Cancer Center at Roger Williams, accepted the Certificate of Excellence from the American Cancer Society on behalf of his colleagues.

“Our recognition today – and from the Commission on Cancer last year – is reflective of the team effort that goes into the care of every single patient who comes to our Cancer Center,” said Dr. Espat. “Exemplary cancer care is delivered when you have a highly experienced and motivated team of surgical, medical and radiation oncologists, along with oncology nurses, laboratory professionals, and support staff. The best care is delivered in a collaborative manner and we strive to do that every day.”

The goal of the Rhode Island Research Breakfast is to create an event for innovators, leaders in business, academia, public policy, and patient advocacy to capture the latest and best thinking about the impact of local cancer research.

“It is important for all of us as individuals, companies, and health care institutions to urge policymakers and leaders from across the life sciences and health system ecosystem to do everything we can to save more lives from cancer,” said Bernard Jackvony, former Lt. Governor and chair of the ACS CAN Research Breakfast. “It is my honor to recognize Roger Williams for receiving the Commission on Cancer Outstanding Achievement Award, which recognizes programs that strive for excellence in delivering high quality cancer care.”

Rhode Island Lt. Gov. Daniel McKee served as this year’s honorary event chair. Along with Roger Williams, others recognized at the breakfast included researcher DR. ADAM OLSZEWSKI, DR. JAMES PADBURY from Brown University, and volunteer and caregiver RAMONE JOHNSON.
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Gaurav Gupta, MD, of the Rhode Island Society of Eye Physicians and Surgeons, shown in back row center, with LDP classmates and Aaron Weingeist, MD, AAO Director, Leadership Development Program.

Gaurav Gupta, MD, Graduates from AAO Leadership Development Program

CHICAGO – On October 17 during the Society Presidents’ Recognition and Awards Session held in conjunction with the American Academy of Ophthalmology AAO 2016 in Chicago, Gaurav Gupta, MD, was recognized for completing his participation in the Academy’s Leadership Development Program XVIII, Class of 2016. Dr. Gupta was among a select group of seventeen participants chosen for the LDP XVIII, Class of 2016, from among a large group that was nominated by state, subspecialty and specialized interest societies.

In January 2016, Dr. Gupta took part in a 2 ½ day interactive session in San Francisco covering a wide variety of leadership and association management topics. The meeting also included a visit to AAO headquarters to hear from the 2016 Academy President William Rich III, MD, CEO David Parke II, MD and Academy Vice Presidents on key priorities for the Academy.

Next was a trip in April 2016 to attend the Mid-Year Forum 2017 in Washington D.C. where Dr. Gupta visited Rhode Island’s members of Congress and their staff to discuss issues important to the medical profession as part of Congressional Advocacy Day. During a dedicated LDP session on Capitol Hill, Dr. Gupta and his LDP colleagues also heard from 2016 US Congressman Paul Tonko (D-NY) about building effective relationships with legislators and how best to advocate on behalf of patients.

Memorial Hospital School of Nurse Anesthesia Graduates 9

PAWTUCKET— Ceremonies for the 50th graduation of the Memorial Hospital of Rhode Island School of Nurse Anesthesia Program took place on October 28 in the hospital’s Sayles Conference Center. Hospital administration, staff, family and friends were on hand to honor the nine graduates.

This year’s graduates are: Mikayla Jarratt of Bellingham, Washington; Lisa Strait of Arizona; Catherine Keyo of Dorchester, MA; Jessica Gregson, Hopkinton, MA; Travis Henderson of Nampa, Idaho; Christopher Manion, Seekonk, MA; Richard Guillaume, Revere, MA; Artur Rozentsvit of New York City, NY; and Micah McRae of Henderson, NV.

Mark A. Foster, CRNA, MA, director of Memorial’s School of Nurse Anesthesia Program, recognized the accomplishments of the nine nurse anesthetists. He noted how the graduates devoted the past 29 months to a comprehensive didactic and clinical curriculum, earning a Master of Science degree in biological sciences/anesthesia.

He also thanked the following individuals who supported the program: Susan Walker, MD, interim anesthesiologist-in-chief and medical director of the School of Nurse Anesthesia; anesthesiologists with Anesthesia Care; Ruth Rollin, PhD, and Mark Jackson, PhD, academic coordinators of Central Connecticut State University; Keith Macksoud and Elena Litmanovich, both faculty, the surgeons and staff in the operating room, Post Anesthesia Care unit, Surgical Place Recovery Unit; and Pulmonary Function Lab at Memorial; Cyndi Hannaway, secretary for the Department of Anesthesia; and the clinical coordinators and adjunct faculty at the following clinical sites- Susan Roessle, CRNA, from St. Luke’s Hospital in New Bedford, MA; Katie Bourski, CRNA, coordinator at Kent Hospital; and Dr. Sana Ata, chairperson and coordinator at Lahey Hospital and Medical Center.

Arthur Rozentsvit, on behalf of the graduates, thanked the administration, Anesthesia Department’s faculty and staff and fellow classmates for their support.
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Robert J. Westlake, MD, honored by Butler Hospital

PROVIDENCE – At Butler Hospital’s fundraising event held Nov. 9, ROBERT J. WESTLAKE, MD, received the 2016 Corporation Member of the Year award, presented each year to one of the 350 corporation members that make up the Butler Hospital Corporation.

Butler’s President and Chief Operating Officer Lawrence Price, MD, presented the award in recognition of Dr. Westlake’s support and advocacy for the hospital’s work and service to the community.

Dr. Westlake has been connected to Butler since 1973, and, during his tenure as a psychiatrist and administrator, is credited with creating Butler’s partial hospital program, and helping to establish the education program for psychiatry residents.

He also served as the vice-chair of adult services.

In his remarks, Dr. Price acknowledged Dr. Westlake for the support he provided during the earlier years of Dr. Price’s career as a psychiatrist and researcher.

Robert J. Westlake, MD, at left, receives the Butler Hospital Foundation’s Corporation Member of the Year Award from Lawrence Price, MD, president and chief operating officer at Butler Hospital.
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Dec. 7, 1941: 75 years ago, Japan attacks Pearl Harbor

*RIMJ launches special features: Doctors at War & Calling All Battle Stations*

**MARY KORR**
RIMJ MANAGING EDITOR

Seventy-five years ago this month, the United States Congress declared war on Japan after the attack on Pearl Harbor on December 7, 1941. Shortly after this ‘day of infamy,’ **DR. PETER PINEO CHASE**, a retired surgeon, became editor-in-chief of the *Rhode Island Medical Journal*.

Wherever Rhode Island physicians served in World War II, Dr. Chase made sure the journal was forwarded to them. He also began two columns, “Doctors at War” and “Calling All Battle Stations,” which reported news from the front. The following are excerpts:

“From somewhere in Germany Capt. Donald L. DeNyse of Cranston informs us that he was in the Normandy invasion, making the landing from an LST [Landing Ship, Tank] on D-day plus 2, and since that time he has been in continuous combat duty with the field service, treating casualties. He now goes on our records as our first member to report to us from inside the Nazi frontiers.”

“We are pleased to report that Major Kenneth G. Burton writes that he is always happy to receive the *Rhode Island Medical Journal*. ‘It has followed me quite regularly considering my many moves.’ Just before and for a couple of months after D-day, he was in a field hospital in England treating casualties from the Channel, the beachheads and later the Continent.”

“On assignment to a hospital following Gen Patton’s Army, Capt. Thomas A. Egan of Providence reports: ‘It is not the surgery that saves the lives of the severely wounded, but the pre-operative care that is given them in the use of penicillin, sulfa drugs and plasma.’”

*RIMJ* also reported on **Commander William P. Davis** after the invasion at Mindoro: “Japanese planes attacked the LST on which Commander Davis was the medical officer in charge and scored a hit…He and crew were trapped on the fantail of the craft as explosions cut off all escape forward. Swiftly administering morphine and caring for casualties, Commander Davis and another surgeon worked at their task until the heat of the deck plates became unbearable and the men had to go over the side. They were picked up by a destroyer escort.”

![The USS Arizona was totally destroyed by the Japanese attack on Pearl Harbor on December 7, 1941.](image1)

Today, at the USS Arizona Memorial, one can look through the windows and see the remnants of the ship and the final resting place of its crew of 1,102.
RIH Unit in Burma

When the war broke out, Rhode Island Hospital (RH) sprang into action and formed the Army's 48th Evacuation Hospital with volunteers from its staff and attending physicians. On Jan. 20, 1943, the RH unit boarded the USS Monticello in California, bound for Bombay. The curtain of the China-Burma-India (CBI) Theater of World War II was about to rise on the RH unit of 69 doctors, nurses and technicians.

The ship, a seized and refitted Italian luxury liner, traveled unescorted and blacked-out. Lighting a cigarette at night meant instant court martial. In his memoir, A Young Surgeon Goes to War, Dr. John S. Dziob describes "the dreaded moonlit nights crossing the Pacific that exposed the ship to possible enemy submarines...the sudden shrieking of the alarm horn sending the crew frantically to battle stations."

Six weeks later, the transport with more than six thousand military and medical personnel arrived safely in Bombay. From there, the RH unit crossed the Indian subcontinent by rail and riverboat, and arrived in Margherita, 40 miles from Burma and 18,000 miles from home.

Ledo Road

The 48th was designated a semi-mobile evacuation hospital of 750 beds, to service Chinese, American, British and Indian troops fighting in Burma under Gen. Joseph "Vinegar Joe" Stilwell and along with Merrill's (Gen. Frank Merrill) Marauders. But the Japanese had them on the run, and Stilwell and the Marauders had retreated into India to regroup.

As a result, the RH unit was declared "surplus," Dr. Irving A. Beck recounted at the Rhode Island Medical Society's annual meeting in 1946. The unit was dispersed.

Some physicians in the 48th accompanied the Army engineers laying the Ledo Road - the lifeline to China - deemed necessary after the Japanese had sealed off the Burma Road. The alternative was flying over the "dreaded Himalayan Hump," Dr. Beck reported.

At Ramgarh

Meanwhile, Dr. Thomas Perry, Jr., along with 18 other RH physicians, backtracked a thousand miles to Ramgarh, the location of the U.S. Army Chinese Training and Combat Command, northwest of Calcutta.

Surgeon Frank Cutts (who left his appendix there) described the Chinese recruits as "poorly nourished, suffering from beri-beri, dysentery, relapsing fever and malaria; they had no conception of sanitation and were constantly spitting on the floor." The latter was of great concern to staff; pulmonary tuberculosis was prevalent among the Chinese.

The tropical heat brought unexpected challenges. "We had no anesthesia machines and open-drop ether at 110 degrees was almost impossible; the ether vaporized so quickly. Fortunately we could get chloroform from the British," Dr. Perry later wrote in the Rhode Island Medical Journal.

The RH unit reassembled a year later, in March 1944, in Ledo, near the Burma-India border. The long-awaited push into Burma by Gen. Stilwell was about to begin and the 48th was deployed.

"The entire hospital and its equipment, including 2 ½-ton trucks, were flown over the mountains into Myitkyina just recently cleared of Japanese. Here another hospital was set up on the Irrawaddy River for American, British, Chinese and Indian troops," Dr. Beck said.

According to Dr. Cutts, "disease consistently produced more disability than did injury or battles casualties." He reported that in the two-year period, which ended on June 30, 1945, the 48th Evacuation Hospital admitted slightly more than 37,500 patients: 7,500 Americans, 2,000 Indians and 28,000 Chinese.