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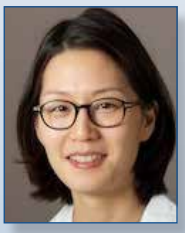
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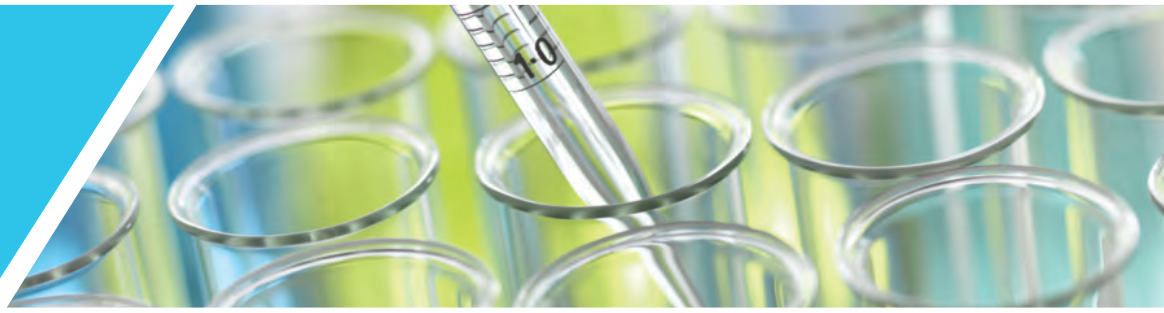

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Standard of Care

JOSEPH H. FRIEDMAN, MD
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I HAVE OCCASIONALLY moonlighted as an expert consultant for legal cases. I am often asked about "standard of care." Malpractice cases rest on harm resulting from substandard care, where the acceptable standard is variably defined. "Standard of care" is the term invoked to determine that benchmark. In Rhode Island, "a physician is bound to exercise the same degree of diligence and skill as physicians in good standing engaged in the same type of practice." (Perry v. Alessi, 890 A.2d 463, 467 (R.I. 2006)). I found another definition of standard of care on the Internet: "the level at which the average, prudent provider in a given community would practice."

I have some difficulty with these definitions because there is such a wide variation in how care is rendered within one community, and certainly between communities. Would one reasonably expect that the level of care in a rural town to be the same as that of a university hospital in a large city? Is the care in Manhattan, New York City, likely to be the same as that in Manhattan, Kansas? But, even within a single community, there is a large variation in how the same problem may be perceived. Yet, the standard of care is considered as a national benchmark. How does one determine an average prudent provider for one community, let alone the whole country?

The data in support of epidural injections of steroids for spinal column pain is woefully thin. If most of my peers nevertheless routinely recommend the treatment, and I do not, is my practice substandard? More challenging, perhaps, if I advised against the treatment but another physician recommended it, and, through some rare mishap, the injection caused harm, would that other physician have practiced substandard care? And what is an "average prudent provider?" Doctors, like the children in Lake Wobegone, are all, at least in their own and their patients' minds, above average.

Physicians in good standing may not practice good medicine. My own view of what the standard of care should mean, knowing that legal definitions often vary considerably from common sense definitions, is the lowest acceptable level of care in a community. Thus the average practitioner in the U.S. should recognize that care below a certain level increases the risk of harm to an unacceptable degree.

I began wondering about the meaning of standard of care when I started thinking about legal experts. We are asked if the patient had been treated in a manner that was below the standard of care, meaning, in fact, would a competent American physician have acted in the same way as the defendant. If one stops to think, it becomes obvious that asking an expert in the field if an average provider is practicing at the acceptable level in the provider's community makes little sense. I can say that the training of neurology house staff would have taught the proper treatment, but some experts are far removed from training house staff. The true expert in determining the standard of care in such a situation is the "average prudent practitioner," and not the expert. What the expert thinks should be routine knowledge may be quite erudite in another field.

The medical expert can attest that the care was suboptimal, that a different medication or a different procedure or diagnostic test administered at the appropriate time would have produced a better outcome, but is unlikely to be a reliable reporter of what constitutes a true standard of care.

I find the distinction between what one considers a term to mean and how the term is legally defined is often unnerving. The omnipresent legalese term in medico-legal issues is, "to a reasonable degree of medical certainty." One states that harm occurred, "to a reasonable degree of medical certainty," because the doctor did or did not do something. In a case I've seen, an expert not only opines with that degree of medico-legal certainty that harm would have been avoided if identified sooner, but also that the patient will, "with a

reasonable degree of medical certainty" have to stop working within 10 years based on studies in which 50% of people with similar problems needed to stop working after 10 years. While I have no problem with giving an opinion that the likelihood of being able to continue working is 50% at 10 years, more or less, depending on the severity of the current condition, what does it mean to have a "reasonable degree" of certainty? Is 50% a "reasonable degree?"

When I consider what "standard of care" means, I ponder the remark made by a United States senator, when considering the credentials of a nominee to the U.S. Supreme Court. The nominee was thought by most to be a rather average thinker and jurist, a person of no particular distinction or merit, chosen, perhaps, because of his blandness. The senator, himself of pedestrian knowledge and accomplishments, supported the nomination by noting that average people need to be represented on the Supreme Court, too.

Using actual experts may sway a jury or a mediator, but it may be a more accurate interpretation of the law to use the testimony of an average, prudent physician, an expert without expertise. ❖

Author

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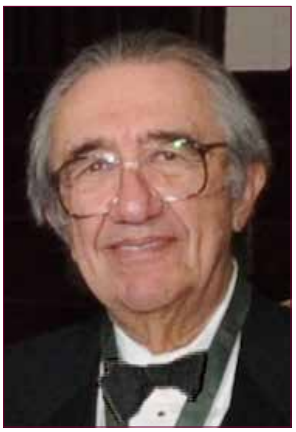
Filming in the ED: A Cautionary Tale

NY hospital settles $2.2M claim over patient-privacy violations suit

HERBERT RAKATANSKY, MD



Lots of people are fascinated by reality TV, including shows recorded live in emergency units (EU). The future of such shows now is in jeopardy. New York-Presbyterian Hospital recently settled a claim for $2.2 million in a suit alleging that an identifiable image of a patient in the EU was broadcast without permission.

As we all know, federal law protects the confidentiality of personal health information (PHI) outside the context of medical care of the patient. HIPAA makes an exception when release of limited PHI is used to identify an unknown patient or to locate family members.

Filming EU reality shows (with permission of the hospital) often occurs without the prior consent of the patient. There may be no time to get consent or the nature of the presentation may make prior consent impossible. Consent is required, however, before identifiable images are used. There are a number of problems with this process.

If post-facto consent is not granted, the film crew still has been privy to the PHI. Additionally, the hospital has granted the crew permission to be in the EU, thus becoming a partner in illegally divulging PHI. What then happens to the recorded images? Who owns them? Are they destroyed? Are they preserved in an "archive" somewhere? If so, who has access?

Absent prior permission, the filming crew should not even be in an area where they might acquire PHI.

Is the patient offered the opportunity to share in the profits from the commercial use of the images? This seems highly unlikely. But what about the hospital? Does it share in the profits? If so, does that motivate it to grant permission for the filming? Does the publicity and resulting renown motivate the hospital to allow this activity?

Permission to record and use images can be granted by an adult patient with the capacity to make decisions. But can a proxy give permission if the patient is unable to do so? Surrogate medical decision-makers have authority to consent to medical treatment. They do not have civil authority however. They may not make financial decisions, for example. Since filming is not a medical issue, designated medical proxies do not have authority to grant permission for it. Only a surrogate with full civil power of attorney, not the limited medical power of attorney, may grant permission for filming. Parents of minor children have such power as do court or personally appointed legal guardians, who specifically have been given such authority.

Even if prior permission is granted by patients to be filmed as part of a reality TV show or as part of a public relations video, HIPAA rules state the media organization would need to be a HIPAA-compliant business associate. It is doubtful that a media company would agree to that.

Though not a HIPAA issue, the health care workers in the EU may feel uncomfortable being recorded by "outside" production crews. Should doctors and others be required to agree?

Images of the patient that are incorporated into the medical record or, with patient permission, are made for training and educational purposes are subject to the same rules applicable to all medical information. Such pictures should be taken only on devices owned or controlled by the institution. These devices should not be capable of directly forwarding the images by text or email. Images belong to the owner of the device. Thus images recorded on devices owned by the institution (or professionals working for the institution) belong to the institution while images recorded on personal devices belong to the individual owner.

However, there is another potential scenario for image recording. Most of us, particularly in the younger (purposely left undefined) generation own a smart phone with a camera. It is very easy for health care workers to take pictures in hospitals and capture images that inadvertently reveal the identity of patients and PHI (a respirator, an IV, a catheter, etc.). Health care professionals and staff

should not create mages containing PHI on personal devices. Both intentional and inadvertent disclosure is a HIPAA violation. Doctors have gotten into trouble for posting supposedly de-identified images in social media, only to find that certain features remained recognizable.

Employees of governmental agencies and private corporations that deal with high security information may not be permitted to use cell phones with cameras in the workplace and in some situations may not even bring them onto the premises. There is thus a small market for cell phones without cameras. This approach is not necessary in the medical environment. But employers and employees should be aware of the risks of taking photos in the medical workplace.

What about families and visitors? We want parents and relatives to be able to photograph newly arrived babies, beloved relatives, etc. A recognizable patient face in the background, however, is a HIPAA violation. Visitors should be informed by appropriate signage of the necessity of confining photos strictly to family and friends.

Additionally, there have been reports of rare surreptitious audio recordings by patients, including instances where the recordings were made while the patient was under anesthesia (recorder hidden in the hair, clothes stored under the stretcher during a colonoscopy, etc.). What if during the procedure, PHI of another patient was revealed? For example, the surgeon might have discussed "Mrs. Jones" who had a condition similar to the patient. The surgeon has every reason to believe that an anesthetized patient cannot hear what is being said. When the patient awakens and hears the recording however, that PHI will be revealed.

Surreptitious recordings should be banned. If a recording is to be made, it should be known to all present. Whether the consent of the doctor is needed is another (controversial) question.

Medical institutions and physician practices should have specific enforceable policies about the confidentiality of images and recordings created in the medical workplace. These rules should be reinforced repeatedly with employees and visibly posted for visitors. As New York-Presbyterian Hospital learned, the consequences of not doing so are costly. ❖

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High Tech Tach: A New Era of Patient-Generated Data

KENNETH S. KORR, MD

As an interventional cardiologist for most of my career, I have become accustomed to a steady stream of new and more improved technologies and therapies – from balloons to stents and atherectomy devices and the ongoing evolution in dual antiplatelet therapy (DAPT) and the newer oral anticoagulants (NOACs). And I have seen similar trends throughout cardiology, in electrophysiology and echocardiography and in other areas of medicine as well. This technology revolution has always been industry-driven and physician-directed. Recently, however, I had the unique experience of the patient bringing me data downloaded from a device via his smart-phone app.

JB has been a long-standing patient of mine since his MI and stent 10 years ago. We have also been in the same tennis group for more than 20 years. He is now 80 and remains robust and active and is a real tech junkie. He has complained of intermittent palpitations for the past year but has had unremarkable EKG, Holter monitor and several event monitor readings. He has been frustrated with our inability to make a more precise diagnosis.

Last week he brought a new tech toy to our tennis session – AliveCor, an FDA-approved, hand-held device about the size of a tongue depressor with metal electrode plates on both ends. When held between the thumbs and forefingers it will record a single-lead EKG that can be downloaded to an iPhone or other smart phone via an app. We all tried it out and got reasonably good quality EKG tracings with variable degrees of baseline artifact, but easily discernible rhythms.

The next morning I received an email from JB with an attachment. At first I thought, well he's just sending me another example of his EKG. But when I opened it, there was an EKG strip of rapid afib @ 130bpm recorded at 11:30 p.m., a few hours after our tennis session and when he was feeling his palpitations. I got another email a few minutes later with another attachment showing afib @ 100 bpm recorded at 6 a.m.

By the time we got JB into the office later that day, he was back in sinus rhythm, but he had brought along several more strips of afib which finally reverted to sinus rhythm at noon. So now, thanks to this device, we had established a firm diagnosis and were able to discuss treatment options. Keeping the tech theme going, I opened up the CHADS2-VASC calculator and took him through the various elements allowing him to calculate his score of 6. This corresponds to a 9.7% annual stroke risk, an obviously high thromboembolic risk and one that warrants long-term anticoagulation.

We moved on to a discussion of the relative risk and benefits of the different anticoagulants. We decided on a once-a-day preparation which I proudly e-prescribed right in front of him. Within a minute he got a text message from his pharmacy stating that his physician had prescribed a new medication but that it would require pre-authorization, a paper and pen process that would take at least a few days. So much for e-prescribing, and certainly not ideal when therapy needs to be initiated immediately. Fortunately my office staff had a first-time, 30-day free drug coupon card and we were able to get him started.

All in all, I was fairly impressed with this simple $100 device which was quickly able to demonstrate an arrhythmia that I had been trying to capture for months and one with significant clinical and therapeutic implications for this patient. I had to ask myself why I was not aware of this device, but it may not be marketed to physicians directly and does not have an easily billable component. In fact, it is more appropriate for the tech-savvy patient with paroxysmal arrhythmias, especially if they travel or are away from conventional medical facilities. Think of it as a more sophisticated extension of patient-generated data, like home pregnancy testing or monitoring of blood glucose or INR levels.

Anyway, I remained very satisfied with the outcome, at least until the next morning when I got another EKG download from JB, just checking in. Fortunately he was in sinus rhythm but he also sent all his recent blood pressure measurements. And today I got a download of his wife's EKG. Patient-generated data and personalized telemedicine here we come! ❖

Author

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Disclosures

None

We are read everywhere

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PHOTOGRAPHY BY MICHAEL MIGLIORI, MD

YUCATÁN, MEXICO

Marianne Migliori, RIMJ graphic designer, paused at the Temple of Kukulcán, the feathered serpent deity, in the pre-Columbian Mayan city of Chichén Itzá.

The pyramid was built between 700–1100 CE and is aligned so that on the spring and autumnal equinoxes, the setting sun casts shadows on the terraced contour creating the illusion of an undulating 'serpent of light' descending the steps, (as shown above.)

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.**

The Evolution of Ophthalmology in Rhode Island

MICHAEL E. MIGLIORI, MD, FACS
GUEST EDITOR

June 2016 marks the 50th anniversary of the graduation of the first Rhode Island Hospital Ophthalmology Residency.

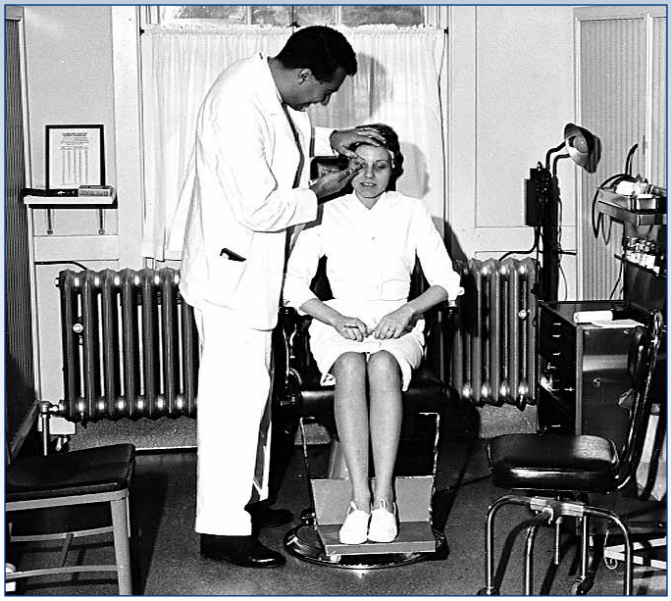
The Rhode Island Hospital Ophthalmology Residency Program was established in 1963, nine years before Brown University's Program in Medicine was created. **DR. ANTHONY BROCCOLI** was recruited as its first ophthalmology resident. When the first medical school class enrolled at Brown in 1972, ophthalmology resident education was provided by a cohort of community-based physicians including **DRS. H. FREDERICK STEPHENS** (Ophthalmologist-in-Chief at RIH), **ALEXANDER CALENDA, CHARLES DOES, JOSEPH DOWLING, JOHN MACIVER, RAYMOND MCKENDALL, LEO PRANIKOFF, NATHANIEL ROBINSON,** and **LIONEL SHEEHAN**, all dedicated to teaching the next generation of ophthalmologists. The program, one resident per year, continued to graduate well-trained ophthalmologists and the number of voluntary faculty continued to grow under the leadership of **DR. ROBERT KINDER**, who became Ophthalmologist-in-Chief in 1978.

DR. WILLIAM TSIARAS became Ophthalmologist-in Chief in 1989, and in 1993, the ophthalmology resident complement was increased to two residents per year. Voluntary faculty continued to provide resident education and supervision.

By 2004, RIH had five part-time ophthalmology faculty members who, along with several voluntary community-based faculty members, provided the didactic education and clinical supervision for the residents. Didactics and teaching conferences at RIH were supplemented by the addition of teaching conferences at the Providence VA Medical Center (PVAMC) in 2006. In 2007, to manage the continued growth of the patient care and the educational missions at the PVAMC, **DR. PAUL GREENBERG**, the Chief of Ophthalmology, became the first full-time Brown ophthalmology faculty member.

In 2013, RIH hired its first full-time faculty member, **WENDY CHEN, MD, PhD**, a pediatric ophthalmologist, followed shortly thereafter by **LENWORTH JOHNSON, MD**, a full-time neuro-ophthalmologist and Deputy Chief, and **MICHAEL MIGLIORI, MD**, full-time Chief of Ophthalmology. **KIMBERLY MILLER, MD**, joined as a full-time glaucoma specialist and Residency Program Director in August 2015. This increase in faculty complement was accompanied by an ACGME-approved increase in the training program to three residents per year.

The current ophthalmology faculty now numbers 45, with five full-time, 15 part-time, and 26 voluntary clinical faculty, as well as one basic science faculty member. This dedicated group of clinicians continues to turn out outstanding residents. Some of our faculty have been with the program for nearly 40 years, and a number of our graduates not only set up practice in Rhode Island, many of them continue to teach the next generation of ophthalmologists.



Anthony C. Broccoli, MD, first graduate of the RIH Ophthalmology residency program in 1966.

Over the last 50 years, ophthalmology as a specialty has evolved as well. The advances in technology with diagnostic imaging, lasers, and surgical instrumentation have made ophthalmic surgery extremely safe and effective. Almost all ophthalmic surgery is now performed as outpatient procedures, and most often under local anesthesia with sedation. Our understanding of ocular diseases has also evolved.

In this issue, **DR. LENWORTH JOHNSON** explores a novel concept in the evolution of understanding the pathophysiology of glaucoma. **DR. LAITH KADASI**, **DR. SAFA WAGDI**, and **DR. KIMBERLY MILLER** discuss a newer paradigm of laser therapy as initial therapy to treat open-angle glaucoma. **DR. ANNA GINTER** and I assess the current research on the mechanisms and targeted therapy of thyroid eye disease. **DR. JAE YOUNG YOU** and **DR. PAUL BOTELHO** describe corneal *in vivo* confocal microscopy, a new technology for the *in vivo* assessment of corneal pathology at the cellular level.

Ophthalmology is a fascinating specialty that combines medicine and surgery, old and new technology, and is constantly changing. It has been a joy to be a part of this training program for the last three decades, and the next 50 years looks even brighter.

Author

Michael E. Migliori, MD, Ophthalmologist-in-Chief, Clinical Professor of Surgery (Ophthalmology), Division of Ophthalmology, The Warren Alpert Medical School of Brown University, Providence

Rhode Island Hospital Ophthalmology Residency through 50 Years

View more photos

Glaucoma as a Neurodegenerative Disease: Why We Must 'Look for the Protein'

LENWORTH N. JOHNSON, MD, MA (HON)

ABSTRACT

For years, clinicians and scientists interested in glaucoma have focused on the anterior segment of the eye and lowering of the intraocular pressure with respect to glaucoma causes and therapies. Yet glaucoma progresses in many individuals despite lowering the intraocular pressure. Herein, the concept of glaucoma as a neurodegenerative disease is presented.

KEYWORDS: actin, Alzheimer disease, cytoskeletal protein, cortactin, glaucoma, human genome, Huntington disease, intraocular pressure, neurodegenerative disease, optic neuropathy, DNA trinucleotide repeat.

INTRODUCTION

Glaucoma is a leading cause of blindness in the U.S. and worldwide (1). Glaucoma is a group of diseases that features a progressive optic neuropathy accompanied by characteristic visual field changes, with or without increased intraocular pressure. Glaucoma has been aptly described as an "*optic vasobaropathy*" indicating that both vascular and mechanical pressure processes contribute to the optic nerve damage and visual loss (2). Risk factors associated with the development of glaucoma include elevated intraocular pressure (> 21mmHg), increasing age, race (blacks more than whites), and a family history of glaucoma. Genes associated with glaucoma have been identified (3,4). Other potential risk factors include diabetes mellitus, hypertension, myopia, cigarette smoking, and alcohol consumption.

GLAUCOMA AND INTRAOCULAR PRESSURE

A primary contributor of glaucoma development is a relative increase in intraocular pressure (IOP). I use the term 'relative' because although a pressure greater than 21 mmHg is considered high, IOPs less than 21 mmHg could contribute to glaucoma (5,6). High IOP results from a decrease in the outflow of aqueous fluid. The aqueous fluid is normally produced by the ciliary body in the eye and exits through the trabecular meshwork and Schlemm's canal. The build-up of pressure in the eye is associated with retinal ganglion cell/optic nerve fiber loss which is exemplified by enlargement of the optic nerve cup-disc ratio and subsequent vision loss (**Figure**). The Ocular Hypertension Treatment Study (OHTS) documented individuals *without* glaucoma, but who have high IOP, have a cumulative increased risk of developing glaucoma at 9.5% incidence in 5 years, or approximately 1–2% cumulative incidence per year (7,8). Older individuals

Figure A. Optic nerve appearance of a patient with glaucoma with optic nerve cup-disc ratio of 0.6.

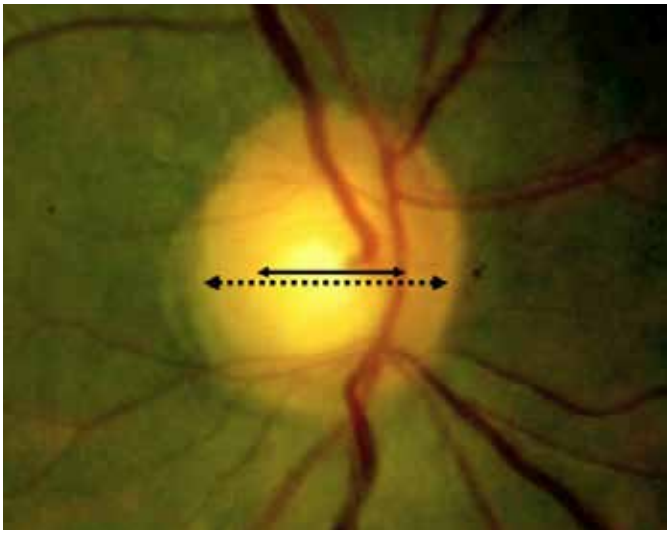
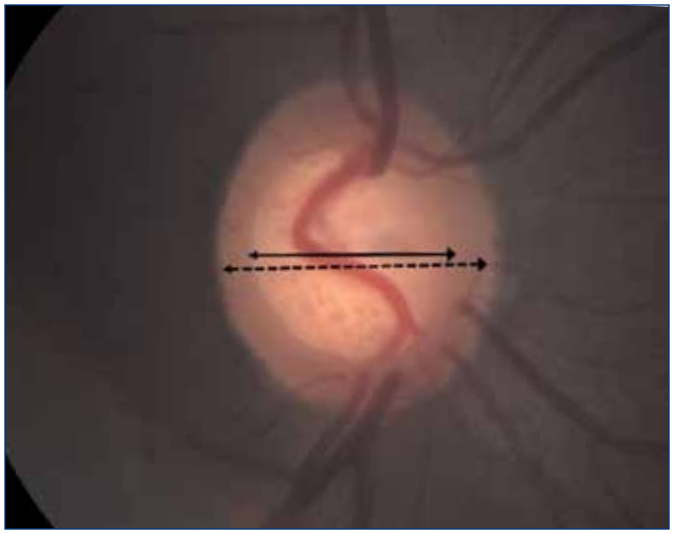


Figure B. Increased glaucomatous cupping from another patient with optic nerve cup-disc ratio of 0.8.



and those with thin (less than 555 microns) central corneal thickness measurements and large vertical cup-disc ratios (greater than 0.3) are more likely to develop glaucoma as the IOP increases.

The Collaborative Initial Glaucoma Treatment Study (CIGTS), Collaborative Normal-Tension Glaucoma Study (CNTGS), Early Manifest Glaucoma Trial (EMGT), Advanced Glaucoma Intervention Study (AGIS), and Glaucoma Laser Trial (GLT) have documented that reducing the baseline IOP by at least 20%, but preferably 30% or more, generally will prevent progression of visual field loss, even in patients with glaucoma who have an initial baseline IOP within the normal range (7–15). Accordingly, methods of lowering the IOP below the aforementioned 20% to 30% target pressure have been the mainstay of treatment for glaucoma, either by topical and/or oral medications, laser surgery (e.g., argon laser trabeculoplasty [ALT], selective laser trabeculoplasty [SLT]), conventional surgery or device placement (e.g., trabeculectomy, drainage implant device placement), or a combination of these therapies. However, despite lowering the IOP by these methods alone or in combination, there is still a cumulative 1–3% per year failure rate among individuals who received these treatments.

IMPORTANCE OF LOOKING FOR THE PROTEIN

Only 4.4% of participants without glaucoma in the OHTS who received treatment to lower the IOP developed glaucoma within 5 years in comparison with 9.5% of untreated participants. The OHTS clinical trial documented participants with high IOP *without* glaucoma at baseline had an approximate 50% reduction in glaucoma conversion at 5 years when IOP was lowered. But this meant the conversion to glaucoma continued in the other 50% of participants despite some of them having had significantly lowered IOP, indicating that IOP is not the sole major factor causing glaucoma. We must look elsewhere. It is my impression that, "*We must look for the protein*."

Most clinicians and scientists interested in glaucoma have focused on the anterior segment of the eye for glaucoma causes and therapies, in particular, evaluation of the trabecular meshwork and aqueous outflow mechanisms. The recognition that glaucoma is a neurodegenerative disease similar to Creutzfeldt-Jakob disease (CJD), Huntington's disease, Alzheimer's disease, Parkinson's disease, myotonic dystrophy, amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease), chronic traumatic encephalopathy (CTE), and spinocerebellar ataxia, is now beginning to gain traction. There is a great need for further investigation of the retinal ganglion cells and their connecting neurons. It is my impression that glaucoma will be identified as a "protein-folding" neurodegenerative disease involving either a trinucleotide repeat (TNR) genetic disorder such as *Poly-GAG* (also called Poly-E) that could occur in actin or its fellow structural cell membrane protein component (e.g., actinin, vinculin, or cadherin), or a variable number tandem repeat (VNTR) genetic disorder as may occur in the cytoskeletal protein cortactin. Why might I suggest this?

REDUNDANCIES IN THE HUMAN GENOME

The haploid human genome consists of 23 chromosomes and 3 billion DNA nucleotide base pairs. The human genome contains approximately 20,000 to 25,000 protein-coding genes, with each gene comprised of approximately 4 exons, and each exon comprised of approximately 250 DNA nucleotide base pairs (16-18). Given that there are 3 billion DNA base pairs of the haploid human genome, then the protein-coding genes comprise only about 1.5% of the total genome. The remainder of the human genome, the 98.5% which previously had been called "junk DNA," is very important as it can be likened to a road map containing the following: regulatory sequences (enhancers, silencers, and locus control regions); promoter sites which bind RNA polymerases; introns; RNA genes (transfer RNA [tRNA], ribosomal RNA [rRNA], microRNA [miRNA], short nuclear RNA [snRNA], short nucleolar RNA [snoRNA], small interfering RNA [siRNA], and other non-coding RNA); and repetitive non-coding DNA which accounts for 50% of the genome.

Genetic defects producing disease may arise from single nucleotide polymorphisms (SNPs) due to DNA nucleotide base pair substitutions, insertions, or deletions. These SNPs cause missense mutations by incorporating the wrong amino acid in the protein sequence (e.g., sickle cell anemia), nonsense mutations by incorporating an early stop signal (coded as TAG, TAA or TGA) causing a shortening of the produced protein, and frameshift mutation by causing a misreading of the 3-letter word DNA sequences due to the insertion or deletion of a nucleotide. Sometimes there could be large-scale rearrangements of the genome resulting in copy number variations (CNVs) which arise from insertion (translocation), deletion, duplication, or inversion of large segments of DNA at the time of meiosis resulting in haploid excess or haploid insufficiency. These CNVs cause genetic effects by increasing or decreasing the gene dose, or by influencing gene transcription and translation through position effects. The SNPs and CNVs alter the gene structure, function, or regulation, causing phenotypic changes or diseases (16-18).

CHARACTERISTICS OF NEURODEGENERATIVE DISORDERS

A relatively common CNV is the sequential repetition of several nucleotide base pairs. When 3 nucleotides are repeated, such as CAG being repeated several times, this is called a triplet nucleotide repeat or trinucleotide repeat (TNR). When 6 or more nucleotide base pairs are repeated, this is called a variable number tandem repeat (VNTR). Everyone has CNVs as a result of us normally having TNRs

or VNTRs. In general, it is when the number of these TNR or VNTR repeats exceeds a certain threshold that a disease is triggered (16-18). Creutzfeldt-Jakob disease (CJD), the prototype of neurodegenerative diseases, is characterized by the presence of a transmissible particle, an abnormal prion PrP protein. Huntington's disease (HD), another classic neurodegenerative disease, is inherited as an autosomal dominant trait and becomes manifest when, on chromosome 4, the normally occurring TNR 'CAG' (which codes for glutamine) is repeated more than 39 times. The normally occurring huntingtin protein now has an abnormal excess of glutamine (polyglutamine, poly-Q) resulting in the pathological hallmark of degeneration and atrophy of the neurons in the striatum and their connecting neurons in the cerebral cortex and other subcortical structures in HD (16-18).

FUNKY PROTEIN CELLULAR DEPOSITS

Like CJD and HD, neurodegenerative disorders have selective destruction of neurons within their associated neuronal network, and deposition of a "funky" or abnormal protein in the affected cell nucleus, cytoplasm, or both. This protein deposition can take the shape of plaques as with Alzheimer's disease, neurofibrillary tangles as with chronic traumatic encephalopathy and Alzheimer's disease, or inclusion bodies (Lewy bodies) in cytoplasm or nucleus as with Parkinson's disease. The "funky" or abnormal protein that is translated from the TNR or VNTR gets cleaved by enzymes in the cytoplasm (16-18). Some of the abnormal protein fragments will enter the nucleus and co-opt the nuclear machinery to make more of itself. The funky protein accumulates within the nucleus, cytoplasm, or both, thereby interfering with the cytoskeleton structure, cell signaling, or mitochondria energy generation machinery, thus killing the cell (18). In the process, the transmissible protein is then passed on to other transsynaptic connecting cells causing selective neuronal destruction. In Parkinson's disease, there is selective destruction of dopaminergic neurons in the substantia nigra and the neurons with which they synapse in the striatum of the basal ganglia and other brain regions. This results in the deposition of proteinaceous inclusion bodies (Lewy bodies) composed of alpha-synuclein protein. In fronto-temporal dementia (FTD) and chronic traumatic encephalopathy (CTE), there is selective destruction of neurons with deposition of tau protein. Alzheimer's disease is characterized by accumulation of amyloid β protein forming senile plaques and tau protein forming neurofibrillary tangles in the nerve cell bodies, resulting in destruction of the cytoskeleton and eventual neuronal death.

There is an increasing body of work documenting glaucoma as a neurodegenerative disease with selective destruction of retinal ganglion cells, the connecting transsynaptic cells in the lateral geniculate nucleus, and occipital cortex (19). Analysis of the vitreous in glaucoma, has shown an excess of glutamate (20). The excess glutamate could be the result of a byproduct of cell death or could be part of the excess "funky" protein that is generated by having TNR or VNTR coding for excess glutamate which then causes cell death. I believe the latter. It is my belief that a potential TNR suspect is actin, a multifunctional protein involved in the cytoskeleton structure, and which normally has a TNR Poly-E (aka Poly-GAG) segment at the beginning of the gene, which could code for the translation of multiple glutamate molecules and abnormal protein folding (21-23). Additionally, a potential VNTR suspect is cortactin, another cytoskeletal protein, which normally has a central 6.5 tandem repeat VNTR consisting of 30 amino acid sequence which also has the potential for coding for the translation of multiple glutamate molecules (21-23). Indeed, recent studies have shown that mechanical pressure on a cell will cause abnormal actin cytoskeletal structural changes, potentially incapacitating the cell (21). In conclusion, it is my impression that glaucoma will be identified as a "protein-folding" neurodegenerative disease. Like other neurodegenerative diseases, *we should look for the protein* in the retinal ganglion cells and their connecting neurons as this hopefully will expand our treatment armamentarium for this group of blinding diseases called glaucoma.

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Selective Laser Trabeculoplasty as Primary Treatment for Open-Angle Glaucoma

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ABSTRACT

Open-angle glaucoma is a silent, chronic disorder which results in progressive and permanent vision loss. Designing the optimal treatment regimen can be particularly challenging in the management of high-risk patients with frequent loss to follow-up or a longstanding history of medication noncompliance. In this article we aim to review fundamental techniques in glaucoma diagnosis and treatment with emphasis on the strengths and weaknesses of selective laser trabeculoplasty, a technique in modern therapy which may mold the future of primary treatment in open angle glaucoma management.

KEYWORDS: selective laser trabeculoplasty, glaucoma, laser surgery

INTRODUCTION

Glaucoma can be defined as a group of diseases that features a progressive optic neuropathy accompanied by characteristic visual field changes, with or without increased intraocular pressure. The most common form, primary open-angle glaucoma (POAG) is a disease that affects more than 2 million individuals in the United States, and is projected to increase to more than 3 million by 2020.[1] It is characterized by a progressive, excavated optic neuropathy and is associated with stereotyped patterns of irreversible visual field loss which can eventually lead to blindness. Although the primary risk factors for this disease include the elevation of intraocular pressure (IOP), the presence or absence of ocular hypertension does not have a role in the definition of glaucoma itself. This article will review our current understanding of glaucoma diagnosis as well as an analysis of the benefits and weaknesses of selective laser trabeculoplasty, a technique in modern therapy which may mold the future of primary treatment in open-angle glaucoma management.

DIAGNOSIS

The identification of glaucoma can be challenging and requires careful assessment of multiple factors and diagnostic tests in order to establish POAG as a definitive diagnosis. Patients are often first established as glaucoma suspects on the basis of risk factors and receive an official designation of open-angle glaucoma following the assessment of IOP, gonioscopy, visual field deficits, and detailed assessment of the optic nerve and retinal nerve fiber layer itself.

Risk Factors

Accepted risk factors in primary open-angle glaucoma include race, specifically African and to a lesser extent Hispanic ancestry, advanced age, elevated intraocular pressure, cup-to-disc ratio, decreased central corneal thickness, and family history of glaucoma.[15-17] Diabetes mellitus has a strong association with open-angle glaucoma, but remains controversial as a risk factor due to conflicting findings as an independent risk factor for disease among major studies.[15,17]

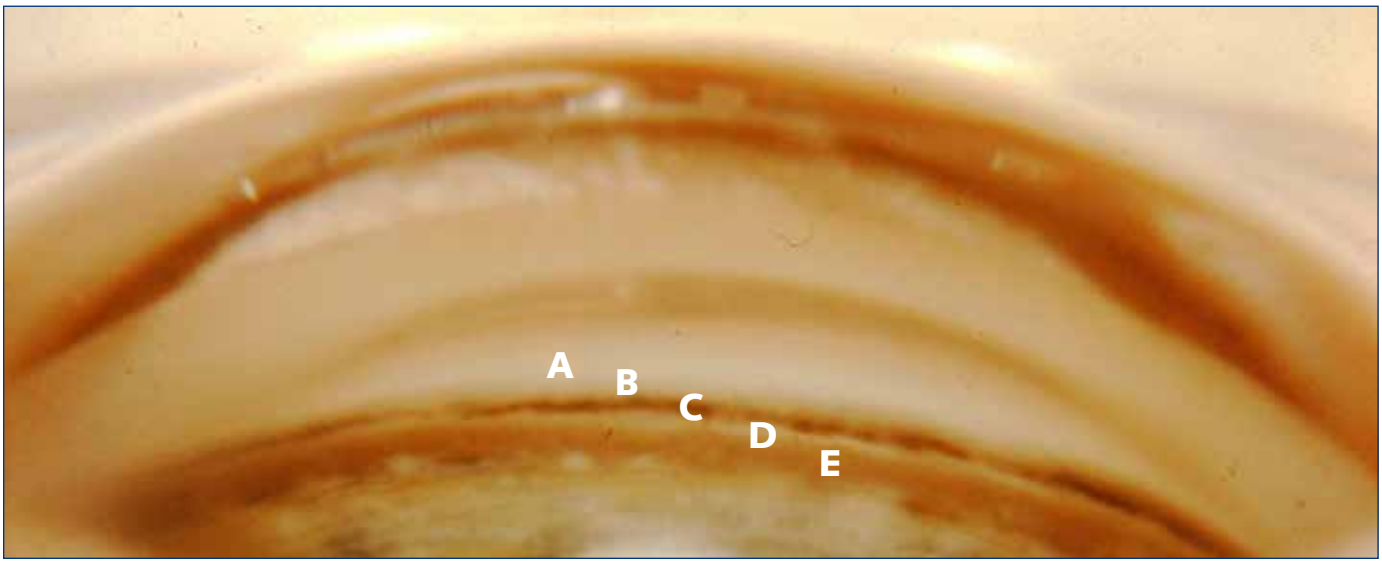
Optic Nerve Assessment

In visualization of the optic nerve using ophthalmoscopy, it is beneficial to evaluate not only the cup-to-disc ratio, but also the distribution of tissue around the margin of the optic disc such as vertical cupping.[15,16] Referral for ophthalmologic consultation in patients with an elevated cup-to- disc ratio or an atypical distribution of neuroretinal tissue at the optic disc will enable further assessment with Optical Coherence Tomography (OCT), an increasingly valuable screening tool which facilitates in the quantification of the retinal nerve fiber layer and ganglion cell layer of the retina, and can result in earlier detection of tissue loss in glaucoma suspects prior to the onset of visual field changes.[3]

Goldmann Applanation Tonometry

The gold standard for obtaining the IOP measurement is via Goldmann Applanation Tonometry (GAT).[20] This test requires the application of a prism mounted on the head of a tonometer against the corneal surface. The tonometer interface viewed by the clinician, adjusting the force applied to the tonometer head until the device indicates the force in mmHg necessary to flatten a 3.06mm diameter portion of the corneal surface. Ocular hypertension is considered pressure greater than 21mmHg. Alternative methods of intraocular pressure measurement are frequently used such as Pascal and ICare tonometry with concordance.[18] These methods are more susceptible to error associated with abnormalities in corneal curvature and central corneal thickness, respectively.

Figure 1. Photograph of the iridocorneal angle during gonioscopy. This image depicts an open angle with visualization of anatomical structures: **A:** Schwalbe's Line, **B:** Nonpigmented Trabecular Meshwork, **C:** Pigmented Trabecular Meshwork, **D:** Scleral Spur, **E:** Iris.



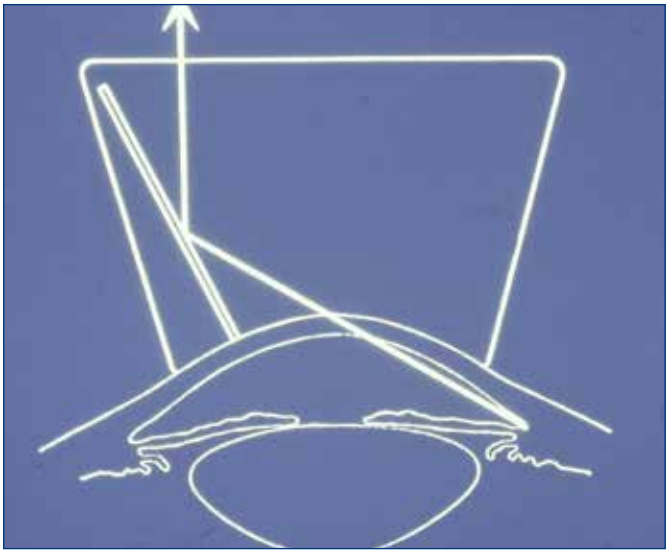
Gonioscopy

Direct visualization of the anterior chamber angle is limited due to the phenomenon of total internal reflection. For this reason mirrors are applied in indirect gonioscopy to reflect light from the iridocorneal angle, allowing complete visualization of the trabecular meshwork in order to identify alternative causes of glaucomatous damage (**Figures 1 and 2**). This analysis includes identifying the presence or absence of neovascularization, or dense pigment deposition as seen in secondary open-angle glaucomas such as pigment dispersion or pseudoexfoliation. Furthermore, obscuration of angle structures can be seen in anatomically narrow angles, predisposing these patients towards angle closure glaucoma.

Visual Field

The gold standard for objective visual field assessment in glaucoma is known as automated static threshold perimetry. Visual field abnormalities do not appear until a substantial volume of ganglion cells are lost.[3,19] Although several alternative methods of visual field measurement are available with variable sensitivity, Humphrey Visual Field testing remains the standard of care for glaucoma patients. Monitoring of characteristic visual field changes and progression remains a mainstay of glaucoma treatment.

Figure 2. Schematic of indirect gonioscopy. This image depicts the method in which gonioscopy can be used to view a reflection of the iridocorneal angle.



MANAGEMENT

Although the pathogenesis of glaucoma remains poorly understood, successful treatment strategies at this time are directed toward lowering intraocular pressure due to a strong association with delay in the progression of glaucoma in treated patients.[2] As a result, predominant trials in open-angle glaucoma therapy over the past several decades have been directed towards comparison among pressure lowering therapy in the form of topical medications, surgery, and laser trabeculoplasty.[4-14] Designing the optimal treatment regimen can be particularly challenging in the management of high risk patients with frequent loss to follow-up or a long-standing history of medication noncompliance.

Traditionally, open-angle glaucoma treatment is initiated with topical medications (**Table 1**), with the eventual consideration of treatment alternatives if there is failure to respond or medication noncompliance.[11] The glaucoma laser trials supported consideration of a "laser first" approach due to the illustration that initial laser therapy was equally effective to topical therapy in direct comparison.[6] These

Table 1. Topical Glaucoma Medications and Systemic Side Effects

Drug Class	Common Topical Agents	Common Systemic Effects
Alpha 2 Adrenergic Agonists	Apraclonidine, Brimonidine	Dizziness, Fatigue, Headache, Insomnia, Myalgia, Nausea, Xerostomia
Beta Adrenergic Antagonists	Betaxolol, Cartelol, Levobunolol, Metipranolol, Timolol	Bradycardia, Bronchospasm, CNS Depression, Heart Block, Hypotension
Carbonic Anhydrase Inhibitors	Brinzolamide, Dorzolamide	Acidosis, Blood Dyscrasias, Depression, Diarrhea, Hypokalemia, Nephrolithiasis
Parasympatho-mimetic Agents	Pilocarpine	Abdominal Cramps, Increased Salivation
Prostaglandin Analogues	Bimatoprost, Latanoprost, Travoprost	Arthralgia, Malaise, Headache

trials took place using an older method of therapy known as argon laser trabeculoplasty (ALT), which has been mostly replaced by a newer and safer alternative, selective laser trabeculoplasty (SLT).

Selective Laser Trabeculoplasty

Due to its extremely favorable safety and efficacy profile, SLT has gained acceptance as a mainstay in open-angle glaucoma management.[4,5] In the coming decade, SLT is likely to become the primary therapy of choice in open-angle glaucoma, due to the safety and cost effectiveness of the procedure, the decreased burden of compliance on patients when compared with traditional therapies, and the ease with which retreatment and traditional operative interventions can be performed in post-procedural patients.

An important consideration in laser therapy safety and cost is the duration of procedure efficacy. Approximately 50% of eyes have been found to fail after SLT following a 2-year period, requiring retreatment.[13,14] Selective Laser Trabeculoplasty remains a relatively young technique with limited data regarding the effects of repeated therapy over a 10-20 year course. These effects must be weighed against the adverse effects of long-term medication or multiple glaucoma surgeries, as patients using topical therapy for long periods of time frequently experience chemical irritation and delayed hypersensitivity reactions such as dermatoconjunctivits medicamentosa. Similarly, traditional glaucoma surgeries have high complication and vision loss rates, making their use limited in early and moderate stage disease. Thus far the side effect profile of SLT compares favorably to those of medical therapy or surgical options, with an absence of systemic adverse effects and elimination of the procedural risks associated with operative monitored anesthesia care or general anesthesia in surgical patients. SLT has been associated with mild post-procedural redness, photophobia, and discomfort in the setting of transient anterior chamber inflammation with reported incidences ranging from 0% to 66%.[7] A transient, 12-24 hour paradoxical increase in intraocular pressure has also been noted, which can be addressed prophylactically with IOP-lowering medications.[4] Isolated observations of very rare complications such as peripheral anterior synechiae, hyphema, and corneal edema have also been described.[8-10] Cost comparison studies directly assessing medical therapy and primary SLT over a 6-year horizon while assuming perfect drop administration efficiency rates have also found savings ranging from $200-3000 per patient, including adjustment for the potential need for retreatment every 2-3 years.[12]

The decreased burden of compliance on patients is perhaps the strongest factor in considering SLT in this lifelong disease. A patient on bilateral maximal medical therapy using a combined ophthalmic preparation such as dorzolamide-timolol in addition to an alpha agonist and prostaglandin analog may be required to administer as many as 6 drops daily for life; if these drops are administered correctly the patient would wait 5 minutes following each when medication administration times coincide. In the presence of comorbid osteoarthritis, incoordination, or postural limitations the decreased efficiency of medication administration will further contribute to increased medical cost due to medication wasting and noncompliance.

CONCLUSION

Open-angle glaucoma is a devastating disease that presents many unique challenges in diagnosis and management. As the technique of SLT matures there will be an increasing body of evidence in support of the use of this technique as primary therapy.

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Disclosures

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The Role of Biological Agents and Immunomodulators in Treatment Strategies for Thyroid Eye Disease: An Evidence-based Review

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ABSTRACT

Graves' Disease is an autoimmune disease where circulating antibodies bind to the thyrotropin receptors on the thyroid gland. These bound antibodies mimic thyroid stimulating hormone without the normal feedback from the anterior pituitary, causing hyperthyroidism and thyrotoxicosis. These antibodies also interact with orbital tissues and cause the characteristic orbital findings of thyroid eye disease (TED). It is not clearly understood why anatomically and physiologically distinct tissues like the thyroid gland and orbit are affected selectively, or why the orbital disease tends to be self-limited. Identifying and understanding these processes is critical to targeting therapy.

In the active phase of the disease patients may experience orbital inflammation, eyelid and conjunctiva edema (chemosis), eyelid retraction, proptosis, ocular motility restriction, and optic nerve compression. Current treatment strategies for the ocular symptoms have been predominantly directed at symptomatic relief. More recently, investigators have concentrated their efforts to better understanding the underlying pathophysiologic processes to direct therapy at these processes. This review examines the current literature exploring a variety of newer therapeutic alternatives, including immunomodulative and suppressive agents, targeted at strategic points of the active-phase TED pathophysiological pathways. Specifically, biological agents including rituximab, adalimumab, intravenous immunoglobulin and others are reviewed with considerations for pathophysiology, extent of literature support, and adverse effects.

KEYWORDS: Grave's Disease, thyroid eye disease, TED, TED treatment options

INTRODUCTION

Thyroid Eye Disease (TED) is the most common extra-thyroid manifestation of Grave's Disease. (1) The annual incidence of TED has been estimated at 16 cases per 100,000 population for women, and 3 per 100,000 for men. (2) It is an immune-mediated disease and is most often associated with the immune thyroid diseases Graves' disease and Hashimoto's thyroiditis, but it can also occur with thyroid carcinoma, primary hyperthyroidism and neck irradiation. Up to 50% of patients with immune thyroid diseases develop TED, and of those, as many as 10% may develop severe inflammation, orbital congestion, impaired ocular motility, or compressive optic neuropathy. (3)

The range of TED treatment options varies depending upon severity, from topically palliative treatments including artificial tears, ointments, or prisms, to immunosuppressive agents such as steroids or cyclosporine, radiotherapy, and surgical decompression in more severe cases. Novel approaches to treatment have included anti-oxidant solutions containing selenium (4) and biological agents like rituximab and anti-tumor-necrosis-factor, among others. (5-7) This review considers the latter category of biological agents, examining briefly the agent, mechanism of action, existing evidence supporting their use, efficacy, and adverse effects. Some consideration will be also given to the role of biological agents in the context of overall TED treatment options, but a detailed consideration of all treatment options is beyond the scope of this biological agent-focused review.

RATIONALE FOR USE OF BIOLOGICAL AGENTS AND IMMUNOMODULATORS

Hyperthyroidism and TED, though temporally concomitant in many cases, may occur over 18 months apart, and even in the absence of one another. (8) Smoking (9) and poor control of the underlying thyroid disease have also being associated with more severe TED. (10) TED typically starts with an active inflammatory progression over 6 to 24 months (**Fig.1**), with expansion of extraocular muscles (EOMs) and surrounding fat (**Fig. 2**), often causing proptosis, impaired extraocular muscle movement, and in severe cases compressive optic neuropathy (**Fig. 4**). (11) Ultimately fibrosis and infiltration of glycosaminoglycans into the extraocular muscles result in the permanent changes seen in the chronic phase of the disease (**Fig. 4**).

Orbital fibroblasts are now considered the primary immunologic target in TED. Fibroblasts from patients with TED have been shown to express inflammatory cytokines, CD 34 and CD40. Pathophysiological studies in TED have also shown increased expression of thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-R1) on these fibroblasts.(12-14) Strategies, in turn, have been targeted at different components of the presumed pathophysiology.

Figure 1. Active phase of TED with eyelid and orbital edema

Figure 2. CT scan showing asymmetric extraocular muscle enlargement in TED

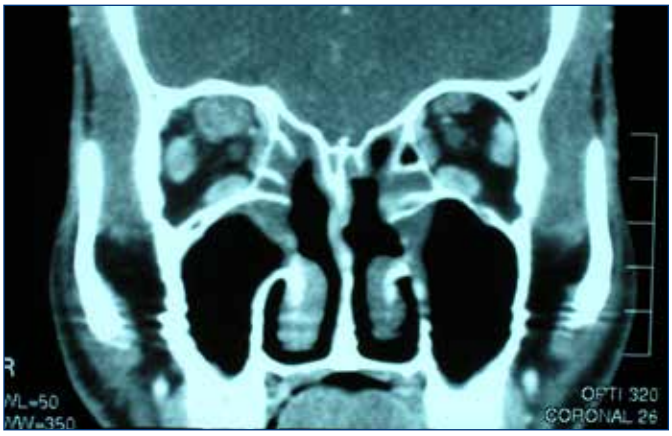

Figure 3. Optic nerve compression from enlarged extraocular muscles

Figure 4. Chronic phase of TED with proptosis and lid retraction

Interestingly, only about one-third of moderate-severe TED sufferers are helped by traditional anti-inflammatory treatment options such as corticosteroids. (1,15) Hence, with the limitations of presently existing therapies and observed inconsistent associations between TED, thyroid disease, traditional anti-inflammatory treatment response, and smoking, the need for other therapeutic strategies is evident. Several such strategies, all at best incomplete and with varying efficacy, are discussed in the following sections on biological agents in TED, along with mechanisms of action and effects.

SPECIFIC AGENTS AND THEIR MECHANISMS OF ACTION

While few or no biological agents are exactly specific for a given target, a few have a thus far recognized preferential target (e.g. rituximab for B-lymphocytes). Hence, for purposes of our discussion below, we consider specific agents with specific targets. This discussion is caveated with the following points: (1) a "pure target" and "pure agent" have not presently been discovered, so some additional effects may occur; (2) no single strategy has shown complete efficacy or "cure"; (3) some of these agents' efficacy is extrapolated from analogous autoimmune diseases but actual human studies are either scarce or non-existent.

Broad-spectrum anti-inflammatory and immunosuppressive agents

Corticosteroids, the mainstay of TED therapy, can be administered orally or systemically as intravenous (IV) infusions. However, current literature favors high dose systemic administration for severe active TED as reported by Kahaly, with greater positive clinical response in 77% of patient receiving IV methylprednisolone treatment vs. 51% of patients treated with oral prednisolone. (16) Similar response results were also reported for treatment of moderate active TED (17) by Aktaran et al with 72% responding to IV steroids vs. 49% responding to oral steroids.

Intraorbital injection of steroids are occasionally used to alleviate the acute orbital inflammation in TED.(18) In a prospective, single-blind randomized study (19) Marcocci et al evaluated cobalt radiation combined with steroid treatment, either administered systemically or locally by retrobulbar injection. Clinical improvement was noted in both groups, but there was significantly greater efficacy of systemic steroids compared to retrobulbar injection (60% vs. 30%) in severe active TED.

Antimetabolites form a group a potent immunomodulators. Azathioprine has not been shown to be of benefit as a single agent (20) but exhibits effectiveness when combined with radiation therapy or steroids. (21, 22) Methotrexate, although not commonly used, is effective as a sole treatment

in patients who failed steroids. (23) Another member of the antimetabolite family, mycophenolate mofetil, was noted to be not only effective but exhibited more effectiveness as a sole treatment than cyclosporine (24); however, the literature regarding this agent remains sparse. Moreover, no comparison of this agent to standard steroid treatment is found in the presently available literature.

The anti-oxidant agent selenium was evaluated against the anti-inflammatory agent pentoxifylline in 159 patients with mild Graves' orbitopathy. The authors noted decreased clinical activity scores of TED in both treatment groups, with significant improvement in quality of life, reduced ocular involvement, and slowed disease progression in the selenium treatment group at the 12-month follow-up. (4) This data suggests selenium oral supplements at a dose of 100ug, twice per day, appears a harmless adjunct to conservative management in early mild stages of TED.

Anti-B-cell agents

Rituximab (RTX), a monoclonal chimeric antibody against the transmembrane protein CD20 on B cells (but not plasma cells), has resulted in improved clinical activity score and efficacy over 18 months in several studies. (25-27) A recent randomized, prospective study evaluating intraorbital injection of rituximab versus high dose of systemic glucocorticoids in the treatment of thyroid-associated orbitopathy demonstrated a therapeutic efficacy of RTX in active disease, even in low doses and locally administered, with the efficacy on the inflammatory component of the disease comparable to that of steroids and seemingly related with the reduction of peripheral CD20+ lymphocytes. (28) Further studies are needed to fully evaluate efficacy and safety of rituximab.

Anti-T-cell agents

T-cells expressing IGF-1 receptors are thought to play an important role in mediating the autoimmune process in TED. Teprotumumab is a human monoclonal antibody that blocks the IGF-1 receptor, initially designed for treatment of solid and hematologic tumors; it is presently also undergoing phase 2 clinical trials in patients with active TED. A recent retrospective, limited sample-study (5) showed that RTX also had an effect on reduction of IGF-1R(+) T cells, coinciding with clinical improvement at 4 to 6 weeks post-treatment.

Meanwhile, a study involving a 12-week treatment period with 11 patients treated with prednisone and 4 using cyclosporine found that combination therapy was better tolerated than prednisone treatment alone, while single-drug therapy with prednisone was found more effective than cyclosporine in patients with severe Graves' ophthalmopathy. (29) A separate study of 40 patients noted some role for cyclosporin with improvement of all signs of endocrine ophthalmopathy while administering cyclosporin-prednisone combination therapy. (30)

Anti-auto-antigen and intravenous immunoglobulin

The hypothesis of an anti-auto-antigen targeting strategy may be supported by a recently published study (31) which showed that thyroid stimulating but not blocking autoantibodies are highly prevalent in severe and active thyroid-associated orbitopathy. Therapeutic measures targeting the autoantibodies may be effective, though such consideration must be cautioned in determining whether the presence of such autoantibodies is truly causal or an epiphenomenon.

A randomized, controlled trial of 19 patients treated with 20 weeks of oral prednisolone vs. 21 receiving 1 g IVIG/kg body weight for two consecutive days every 3 weeks (repeated 6 times) noted a comparable successful outcome between the two groups (at 62-63%), with responders noted to have improved proptosis, visual acuity, intraocular pressure, lid aperture, and eye muscle area. In addition, thyroid antibody titers were reduced markedly in the IVIG group. However, the incidence of side effects was noted to be more severe in the steroid group, for which the authors suggested IVIG may be preferable to steroids for TED. (32)

Plasma Filtration

A separate randomized study of 20 patients comparing IV methylprednisolone alone or in conjunction with plasma filtration(33) found that while both groups improved their clinical activity scores, the change occurred more rapidly in patients treated with plasma filtration.

Biologic response modifiers

Various anti-cytokine-specific strategies have been evaluated in patients with different severity of TED. For example, in a small (10 consecutive patients) study, the TNF receptor blocker etanercept was found to improve the clinical activity score significantly for those suffering from mild-to-moderate TED. (7) One case showed infliximab (monoclonal antibody against TNF) being successfully used in a sight-threatening TED resistant to oral steroids. (34) Anti-TNF medication adalimumab (a fully human monoclonal antibody against TNF) may have a limited role in TED with prominent inflammatory symptoms, as noted in a small sample observer-blinded. (35)

Tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, mainly used in treatment of severe rheumatoid arthritis and juvenile idiopathic arthritis, proved to be effective when used in steroid-resistant active, severe TED in a small study of 18 patients, with improvement in proptosis in 72% of patients, extraocular motility in 83% of patients, and diplopia in 54% patients. (36) However, this is a novel drug, and hence minimal data is available.

Anti-Cell-Adhesion

A prospective, randomized, controlled trial of colchicine (1.5 mg/day) vs. prednisone (0.75 mg/kg/day) in 22 patients during the inflammatory phase of Graves' ophthalmopathy found improved clinical activity scores in 68% of the colchicine

treated patients, with signal intensity on MRI also noted to be improved; side effects were prevalent in the steroid group but absent in the colchicine group. (37) It has been proposed that colchicine is specific to neutrophil and endothelial cell adhesion, modulating chemokine and prostanoid production. (38)

Future Considerations

Not all novel treatments have shown promise. Somatostatin analogs, which may play a role in the development and regulation of T cells, have been shown to offer no improvement in TED patients in randomized controlled trials. (39-42) An interesting side effect of prostaglandin F2-alpha eye drops (bimatoprost), an agent used to treat glaucoma, is the development of orbital fat atrophy, termed Prostaglandin Associated Periorbitopathy. (43) This eye drop is undergoing a randomized, controlled, double-blind crossover trial in thyroid eye disease to assess its effect on the orbital fat of TED patients.

Animal models for auto-immune thyroid eye disease are limited, but some success has been achieved and described. (44) Though beyond the scope for detailed consideration in this review, such models, if they can accurately be extrapolated to human disease, could be very valuable in creating effective treatment modalities.

CONCLUSIONS

The data considered above suggests a role for different, newer agents, exemplified by wide-ranging predecessors such as selenium's anti-oxidant properties (for milder TED) to anti-inflammatory and generally immunosuppressive properties of steroids or cyclosporin. Specific biological agents such as RTX have shown improvement, with IVIG and even anti-TNF medications having potential roles in specified symptoms. Patient selection for specific therapy, as well as a broader understanding of pathophysiology will likely lead to creation of more targeted therapies. These, in turn, must be evaluated in properly designed prospective, double-blinded, randomized, controlled trials.

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Corneal *In Vivo* Confocal Microscopy: Clinical Applications

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ABSTRACT

In vivo confocal microscopy (IVCM) has become a widely accepted imaging technique to study the human living cornea. It provides a unique opportunity to visualize the corneal tissue at the cellular level without damage and longitudinally observe its pathologic and normative changes. With rapidly evolving technology, there has been an abundance of interest in maximizing its potential to better understand the human cornea in health and disease. This is evidenced by a growing literature analyzing acquired and inherited corneal and also systemic diseases using corneal IVCM. This article provides a narrative review of IVCM and its applications.

KEYWORDS: *In vivo* confocal microscopy, cornea, infective keratitis, corneal dystrophy

INTRODUCTION

In vivo confocal microscopy (IVCM) is a non-invasive imaging tool that enables an *in vivo* examination of the cornea at greatly enhanced magnification. Recent advances have broadened its application in both research and clinical realms as they allow fast acquisition of high resolution images of living cornea and its microstructures. This article provides an overview of current research and clinical applications of this technology.

Optical principle of confocal microscopy

The main advantage of confocal microscopy is its ability to obtain images from selected depth by optical sectioning.[1] It is achieved by focusing a light source through a slit, or an aperture, on a small area of the tissue and analyzing the reflected light only from the selected focal plane. The light from the out of focus planes is attenuated. As the scan progresses serially through various depths of the cornea, multiple optical sections are acquired, creating an *en face* image of corneal layers and its microstructures such as Langerhan cells, sub-basal nerves, keratocytes and endothelial cells.[2] (**Figure 1**)

The concept of confocal microscopy was first patented by Marvin Minsky in 1957 to study the brain neural cells.[2] It was subsequently applied in various facets in ophthalmology, namely retinal and optic disc confocal scanning laser ophthalmoscopy. After numerous IVCM studies in *ex vivo* human eyes and *in vivo* rabbit eyes, the first *in vivo* images of the human cornea were obtained by Cavanaugh *et al.* in 1989. They demonstrated the confocal visualization of epithelium, basal lamina, Bowman's layer, stromal nerves, pre-Descemet's membrane and endothelium in living cornea.[3] More importantly, it portended a new paradigm to bridge histopathologic knowledge to the living tissue and study the dynamic nature of the living eye.

Thus far, three main commercial confocal systems have been developed for *in vivo* corneal imaging; the Tandem Scanning Confocal Microscope (TSCM), the Slit Scanning Confocal Microscope (SSCM) and the Laser Scanning Microscope (LSCM).[1,2,4] The first real-time TSCM was introduced in 1989. It was based on the modified Nipkow spinning disc technology which used a metal disc with multiple pinholes of 30 microns in size. The metal disc was rotated at high speed, allowing rapid acquisition. The small pinhole also provided a thin field of depth; however, it limited the light output that reached the detector to less than 1%.[3] Then, SSCM was introduced in 1994 with improved light output throughout and faster acquisition time; however, at the cost of axial resolution.[4] The axial resolution of SSCM ranged from 8 µm to 25 µm, in comparison to 9 µm to 12 µm in TSCM.[4] LSCM was first introduced in 2003, comprised of Heidelberg retina tomograph (HRT) and Rostock Corneal Module.[4] It rapidly scans a 670nm-diode laser beam and creates a high resolution image of 384 x 384 points in a 400 µm. This device provides a greater contrast than TSCM or SSCM with the superior axial resolution of 4 µm, but it is not as user-friendly as SSCM.[4] Unfortunately, the quantitative measurements between different types of machines are not comparable due to differences in contrast and sectioning thickness. TSCM is no longer commercially available.

Clinical application of IVCM

The role of corneal IVCM in the clinical setting has expanded over the last three decades. IVCM characteristics of acquired and inherited corneal pathologies such as infectious keratitis of many organisms and Fuchs' endothelial dystrophy have been extensively studied.[4,5] Further, the quantification of IVCM parameters, including cell densities (epithelium, keratocytes and endothelium), sub-basal nerve plexus density, number, length, tortuosity and reflectivity and anterior stromal backscatter were tirelessly pursued.[4,5] Through these

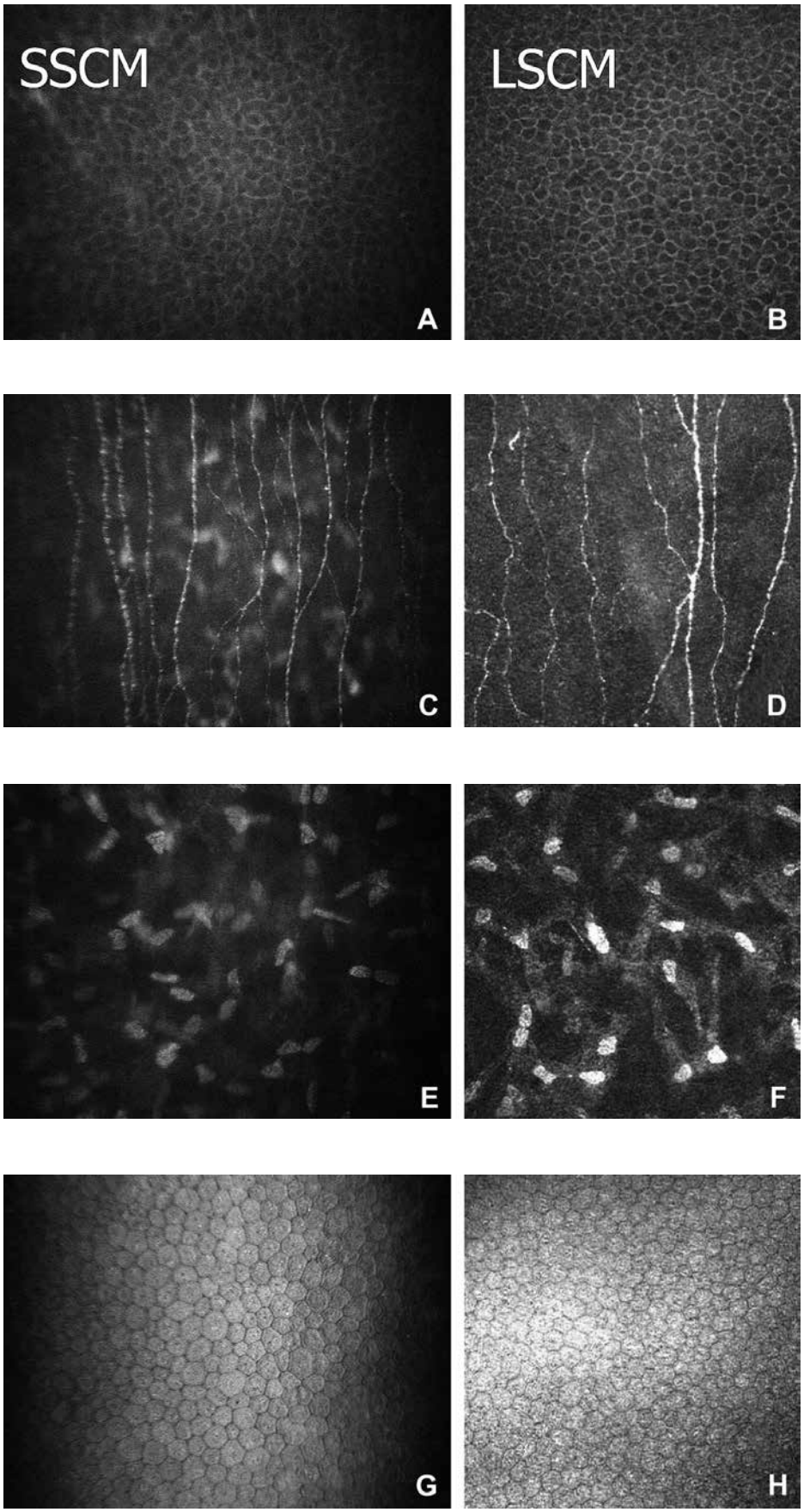

Figure 1. Representative IVCM images of normal cornea using SSCM (Confoscan 4, NIDEK, Gamagori, Japan) and LSCM (Heidelberg Retina Tomography II Rostock Corneal Module, Heidelberg Engineering, Heidelberg, Germany).

A and **B** demonstrate the corneal epithelium using SSCM and LSCM, respectively.

C and **D** show the sub-basal nerve plexus between basal epithelium and Bowman's layer.

E and **F** show the corneal stroma.

G and **H** show the corneal endothelium.

SSCM images are sized 460 x 345 mm, LSCM images are cropped to 345 x 345 mm.

(With permission. Niederer R, McGhee C. Clinical *in vivo* confocal microscopy of the human cornea in health and disease. *Progress in Retinal and Eye Res*. 2010;29:30-58)

endeavors, we have gained a useful insight into corneal infectious and inflammatory disease, dystrophy and wound healing.

Infectious keratitis

The role of IVCM in the clinical setting has been the most highlighted in the management of infectious keratitis. While microbiology diagnosis via corneal scrape or biopsy remains the gold standard, IVCM renders early diagnosis and initiation of targeted antimicrobial therapy.

This is particularly useful in challenging cases such as contact lens-related keratitis.[4,6,7] Acanthamoeba cysts measure 15–28 µm; the tropozoites measure 25–40 µm; fungal hyphae measures approximately 6 µm.[4] They can be visualized using IVCM directly. In a prospective, double-masked, observational study that included 103 microbiologically-proven Acanthamoeba and fungal keratitis cases, the sensitivity of IVCM in the identification of Acanthamoeba cysts and fungal elements was 88.3% and specificity was 91.1%.[7] This early diagnosis may have a profound impact on visual outcome.[8,9,10] The American Academy of Ophthalmology reported level II

evidence for the adjunctive role of IVCM in the diagnosis of Acanthamoeba keratitis.[11]

The sub-basal nerve and dendritic cell densities in herpetic simplex keratitis and herpes zoster ophthalmicus have also been studied extensively. The loss of sub-basal nerve density has been shown to be a prominent feature in IVCM along with increased dendritic cell density in the basal epithelium and squamous metaplasia.[12,13] The loss of sub-basal nerve correlates with the clinical loss of corneal sensation.[13] These characteristics can help diagnose herpetic keratitis in complex cases.

The sub-epithelial infiltrates in patients with epidemic keratoconjunctivitis has been associated with increased dendritic cell density in the basal epithelium and Bowman's layer.[4] On the other end, the use of IVCM in bacterial keratitis has been limited, as the organisms are generally beyond the resolution of IVCM.[4]

Post-surgical changes

IVCM has contributed greatly in understanding the healing process of the cornea after refractive surgeries. Using IVCM, we learned that it may take up to one month for epithelial architecture to return to normal following photorefractive keratectomy (PRK).[4] Also, the sub-basal nerve density is not fully recovered until two years after PRK and five years after laser-assisted in situ keratomileusis (LASIK).[14] Additionally, IVCM has been instrumental in demonstrating the efficacy of using mitomycin-C with PRK.[15] Post-PRK haze is correlated to increased cellular reflectivity due to activated keratocytes. Gambato et al. performed a randomized controlled study of corneal wound healing following PRK and observed a reduction in the IVCM appearance of activated keratocytes and clinical corneal haze with application of mitomycin C in high myopic patients.[12]

Most of our current knowledge in cellular changes after corneal transplant come from animal models or *ex vivo* issues. Real-time observation of wound healing process after various keratoplasty techniques has become possible with IVCM. A longitudinal study found that only 53% of subjects re-innervated with anterior stromal nerves in the central cornea at 12 months following penetrating keratoplasty and the regenerated nerves have abnormal morphology such as increased tortuosity.[16]

IVCM has also been implicated as a potential tool to monitor subclinical cellular changes after corneal transplant.[17] A prospective observation study monitored the keratocyte counts in the anterior, middle and posterior stroma for two years following penetrating keratoplasty and demonstrated that the increase in the AK counts was seen two months before the clinical diagnosis of rejection. This was followed by the normalization of keratocyte count after intensive anti-rejection regimen, comparable to the group that did not have clinical signs of the graft rejection.[17] The ability of IVCM to detect signs of rejection prior to clinical signs will allow early diagnoses, treatment of corneal rejection and successful corneal transplants.

Corneal dystrophy

The use of IVCM has enabled us to visualize the pathophysiology of many corneal dystrophies *in vivo*. While *ex vivo* specimen allowed the studies of end-stage disease, we are now able to follow the changes occurring over the course of the disease. We are also able to screen the affected family members for some inheritable corneal dystrophies.[4] IVCM is also being used to newly classify the severity of corneal dystrophy. A good example is seen in Fuchs' endothelial dystrophy.[18] The traditional grading, based on the extent of guttata and corneal edema, is inadequate in the era of DSAEK and DMEK. IVCM has demonstrated early factors associated with increased anterior corneal backscatter, abnormal sub-basal and stromal nerve density and decreased anterior keratocyte densities.[18] These parameters are being studied with the goal of achieving an objective method of assessing disease severity.

Additionally, in complexes cases of corneal dystrophy, IVCM is increasingly utilized to diagnose one or more diseases.[19]

Peripheral neuropathy

The cornea is the most densely innervated part of the human body. It has emerged as a promising region to study systemic peripheral neuropathies.[2] Using IVCM, we can quantify sub-basal nerve damage as a surrogate for the severity of peripheral neuropathy.[2] This allows early detection, diagnosis and treatment response. Its possible role in detecting and managing nerve damage has been studied in diabetes, Parkinson's disease, amyotrophic lateral sclerosis and chemotherapy-induced peripheral neuropathy.[20] Studies have shown that decreased subbasal nerve density is associated with symptoms of peripheral neuropathy. Further, the loss in corneal subbasal nerves precede any clinical signs or symptoms of neuropathy, retinopathy and nephropathy.[20] Interestingly, IVCM has been shown to detect early nerve regeneration after pancreas transplantation in patients with type I diabetes. This is an especially exciting application of IVCM, as it can potentially benefit a large number of patients.

FUTURE DIRECTION

IVCM has broadened our understanding of the cornea in a profound way, offering a unique window to examine *in vivo* cornea tissue in health and disease and quantify corneal pathology. It has yet to reach its peak. Advancing technology in software and engineering, standardized acquisition, establishment of baseline values and development of software for automated analysis are some of the areas that will increase its accessibility and application in both research and clinical arenas. Regardless, with rapidly evolving technology, it continues to be a powerful clinical tool in vision science.

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The Preparticipation Evaluation and Cardiovascular Screening in Young Athletes: Considering the Pros and Cons

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ABSTRACT

Sudden cardiac death in young athletes is an uncommon but devastating event. The preparticipation evaluation affords an important opportunity to screen for cardiovascular disease and other health conditions but has certain limitations in its existing form. This article provides an overview of current screening practices and outlines the argument for and against the addition of a 12-lead electrocardiogram to the preparticipation exam in an effort to prevent sudden cardiac arrest.

KEYWORDS: Preparticipation exam, sudden cardiac death, athletes, 12-lead electrocardiogram

INTRODUCTION

The health-related benefits of exercise are well known. However, a small segment of the population is at risk for exercise-associated sudden cardiac death (SCD) due to a variety of congenital, inherited, or acquired cardiovascular conditions. Atherosclerotic coronary artery disease is the most common cause of SCD in athletes over the age of 35. (1) Younger athletes are at greater risk from structural heart disease, such as cardiomyopathies and other congenital abnormalities. Although consensus recommendations and standard guidelines were developed by the American Heart Association for athletic Preparticipation Evaluation (PPE), these guidelines are inconsistently applied across the United States. Rhode Island is the only state that does not require any form of examination. (2) Nonetheless, the PPE is a widely accepted screening tool used to identify athletes at risk for SCD and other sports injuries, so that appropriate preventive measures can be taken. The addition of the 12-lead electrocardiogram (ECG) to preparticipation screening is the subject of considerable debate within the sports medicine community. Here we will briefly present both sides of the argument as it relates to youth athletes.

Existing methods of screening are effective for ensuring safe participation in youth and interscholastic athletics.

PRO (KHAUND): Sudden cardiac death is reportedly the leading cause of death of athletes during sporting activity with estimates ranging from 0.5-3/100,000 athletes per year. (3-5) In the United States, preparticipation exams typically follow the AHA recommendations for a cardiac screening history and exam. (**Table 1**) Based on the questionable specificity of further testing, coupled with concern for maintaining a cost effective approach, this has long been considered the standard of care. Given the existing lack of uniformity in this country regarding preparticipation evaluation, I suspect the addition of further testing will present inherent challenges. PPEs are often provided at nominal cost, without insurance involvement, in order to attract student-athletes to the screening process. To accomplish a broad outreach, PPEs are also commonly offered as large-scale and community-based programs which rely heavily on volunteer medical personnel. The addition of further testing that might increase cost and liability will only detract from our current efforts. Although data from abroad suggests that added testing can identify more athletes at risk, this does not appear to be practical within the current healthcare landscape. I strongly believe that our first priority is to engage the student-athlete in the healthcare system. As it stands, taking a thorough history and performing a proper exam must serve as the initial approach to screening and can provide useful information

Table 1. AHA Recommendations for Preparticipation Cardiovascular Screening of Competitive Athletes (1)

Personal Medical History
1. Exertional chest pain or discomfort
2. Unexplained syncope or near-syncope (particularly concerning when related to exertion)
3. Excessive exertional and unexplained dyspnea/fatigue, associated with exercise
4. Prior recognition of a heart murmur
5. Elevated systemic blood pressure
Family History
6. Premature death (sudden and unexpected) before age 50 due to heart disease, in ≥1 relative
7. Disability from heart disease in a close relative <50 years of age
8. Specific knowledge of certain cardiac conditions in family members (i.e., hypertrophic cardiomyopathy, ion channelopathies, or other clinically important arrhythmias)
Physical Examination
9. Heart murmur (auscultation is recommended in both supine and standing positions)
10. Femoral pulses to exclude aortic coarctation
11. Physical stigmata of Marfan syndrome
12. Brachial artery blood pressure (sitting, preferably in both arms)

Adapted from Recommendations and Considerations Related to Preparticipation Screening for Cardiovascular Abnormalities in Competitive Athletes

regarding other medical conditions and risky behaviors. Only when we can consistently achieve this standard should we turn our attention to broadening the methods of screening.

CON (FEDEN): Sudden cardiac death in healthy young athletes is a rare but catastrophic event, with devastating impact on the family and the community. In an effort to enhance the safety of athletic participation, cardiovascular screening recommendations from the American Heart Association include a focused personal and family history, and a physical exam directed at identifying cardiovascular abnormalities that might predispose to sudden cardiac arrest. While this is a reasonable starting point, lack of standardization is a major limitation to current screening practices. Furthermore, available research demonstrates the value of adding electrocardiography to the preparticipation evaluation. Corrado and colleagues studied athletes in Italy over a 25-year period (1979–2004) and reported an 89% relative reduction in sudden cardiac death in athletes screened with history, physical, and 12-lead ECG. (6) This reduction resulted from the improved detection of cardiomyopathies and disqualification of athletes at risk. Even without the incorporation of the ECG, I agree with Dr. Khaund that improved standardization and application of current practices would certainly improve our existing approach to preparticipation screening.

The preparticipation physical examination is our best screening tool for detecting cardiovascular disease in young athletes.

PRO (KHAUND): An optimal screening test incorporates cost effectiveness with a validated test that has optimized specificity (e.g., a low false-positive rate). As it stands in 2016, the growth of sports medicine as a field has helped to enable PPEs to become best practice. Relying on medical personnel, many of whom donate their time and services toward this goal, to reach out to the athletic population is of paramount importance. We must remember that an effective screening test is one that caters to the general population. Added diagnostic testing might narrow the cohort of professionals qualified to perform these evaluations, while also making it more difficult to recruit other volunteers due to increased liability exposure. Additional screening measures could be considered only with the understanding that we must continue to broaden our outreach. The current PPE as it pertains to cardiovascular disease is best suited for our existing healthcare resources. As studies and standards evolve regarding the use of further diagnostic testing, this may one day change. However, until we accomplish our primary goal of ensuring that all athletes undergo preparticipation evaluation in some form, adding further diagnostic testing would be akin to "putting the cart before the horse."

CON (FEDEN): An effective screening tool must balance high sensitivity with acceptable specificity. However, several studies, including that by Maron et al., have demonstrated poor sensitivity for the detection of cardiovascular abnormalities by history and physical exam alone. Conditions that predispose to sudden cardiac death are often clinically silent, and up to 80% of deaths may occur without warning. (7) In the United States, hypertrophic cardiomyopathy is the most common cause of sudden cardiac death in young athletes. (1) Although there may be clues in the family history or a systolic murmur auscultated on exam, an abnormal ECG is a more reliable finding. Echocardiogram is the gold standard for diagnosis, since the resting ECG is abnormal in up to 95% of cases, and a normal ECG has negative predictive value approaching 100%. (8,9) With the additional advantage of detecting cardiac conduction abnormalities, the 12-lead ECG is an arguably superior screening tool for the identification of otherwise silent cardiovascular conditions.

ECG screening of young athletes is necessary to detect cardiovascular disease and prevent sudden cardiac death.

PRO (FEDEN): The repercussions of sudden cardiac death in the young athlete are far-reaching, and all available resources should be used for preventive efforts. Though we cannot expect to eliminate this problem altogether, even one preventable death might be considered one too many. Our current practice of screening for clinically silent conditions with history and physical, even when performed in systematic fashion as outlined by the AHA, is poorly sensitive and inadequate. The Italian experience offers compelling evidence that the simple addition of 12-lead ECG to the preparticipation evaluation improves diagnostic sensitivity and reduces the incidence of sudden cardiac death. The most common causes for sudden cardiac death in the athletic population under age 35 are frequently associated with ECG abnormalities. In addition, other inherited conditions may be discovered with a resting 12-lead ECG. Identification of those at-risk allows for selective disqualification, appropriate intervention, and overall risk reduction.

CON (KHAUND): There is no doubt that missing one preventable death is too many. However, we need to consider the cost-benefit analysis. Until we can achieve the primary goal of consistent and broad outreach to the athletic population with PPEs, mandatory ECGs will likely detract from that effort. It is important to understand the role of the PPE as a way to engage the athlete in the health care system. The ability to speak with and counsel athletes in general has significant implications for decreasing morbidity and mortality from all causes. While we may identify the rare cases of cardiac disease in a specific population, I would venture to say that broadening our outreach will improve all-cause morbidity and mortality. Although the screening ECG has been shown in numerous studies to help identify those with underlying cardiovascular disease, I do not believe that the existing PPE is ready for added screening measures at this point in time. The PPE is further meant to afford an opportunity for contact with athletes before participation to help optimize their overall health. The downstream consequences of investigating false-positive studies – cost, access to care, and psychological implications for the athlete – are not insignificant. The threat of more complicated and/or costly evaluations may result in less compliance and, therefore, narrowed outreach.

Addition of routine ECG screening to the preathletic evaluation is feasible.

PRO (FEDEN): Despite the evidence demonstrating benefit to screening athletes with 12-lead ECG, opponents argue against the cost-effectiveness and feasibility of implementing a large-scale program. Concerns over ECG screening often focus on the financial burden associated with the additional investigation of false-positive ECGs, which is reported to be as high as 40%. (10) However, Marek and colleagues have successfully delivered such a program in the Chicago area using physician and trained community volunteers. (11) They screened 32,561 high school students over three years and found only 2.5% with abnormal ECGs requiring further evaluation. Unfortunately, the number of false-positives could not be determined since subsequent evaluation was directed by primary care physicians. Other critics cite the difficulties with ECG interpretation as a contributing factor to high false-positive rates, but Drezner and colleagues have reported that standardized ECG criteria allow for accurate interpretation with a sensitivity of 94% and specificity of 91% across physician specialties. (12) Although there is clearly a cost associated with further work-up, screening costs are minimal when there is an interest and investment from the local community.

CON (KHAUND): The addition of ECG screening to the preparticipation exam is not feasible in the United States at this time. The cost of including the ECG would likely decrease the availability of the PPE to the population at large. Furthermore, the liability associated with ECG interpretation and follow-up might discourage certain medical personnel from offering their services. At present, the primary focus should remain on access to PPEs for athletes. As future research elucidates the true sensitivity and specificity of ECGs as a screening tool in the United States, the pressure will likely mount to include ECGs in the screening process. Before this can occur, however, the logistics of obtaining ECGs on a large scale and standards for interpretation will need to be further established. An endorsement from the American Heart Association will also be crucial to this process. The pressure is clearly building in the United States to follow our European colleagues, and it would not be surprising to see changes in the coming years with organizations like the American Medical Society for Sports Medicine leading the charge.

CONCLUSION

The identification of young athletes with cardiovascular conditions at risk for sudden cardiac death is an important issue confronting the athletic and sports medicine communities. Preparticipation screening with the history and physical exam is supported by the AHA but may not be sufficient for the detection of clinically silent conditions that predispose to sudden cardiac death. The experience of our Italian colleagues suggests that the addition of the 12-lead ECG improves sensitivity and reduces the incidence of sudden cardiac death, but controversy surrounds the cost-effectiveness and feasibility of similar screening methods in the U.S. Regardless of the screening approach and the risks, we must appreciate the importance of athletic participation and remain committed to ensuring the health and safety of athletes of all ages.

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Etiology of symptomatic urethritis in men and association with sexual behaviors

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ABSTRACT

INTRODUCTION: Gonorrhea and chlamydia are sexually transmitted infections (STI) that are the most common causes of urethritis in men. The role of specific sexual behaviors and presentation of urethritis is often overlooked.

METHODS: Data was retrospectively reviewed on all men presenting at the major STI clinic in Providence, Rhode Island. Predictors of gonorrhea and chlamydia infection were modeled using a generalized model assuming a binary distribution.

RESULTS: Of the men with urethritis, 27% had chlamydia, 13% gonorrhea, 3% both, and 63% neither (non-gonococcal, non-chlamydial urethritis). MSM were more likely to test positive for gonorrhea than MSW (25% of MSM versus 6% of MSW; $p<0.01$).

CONCLUSIONS: MSM with urethritis were much more likely to test positive for gonorrhea which may be due to increased risk behaviors and spread within concentrated sexual networks. A large number of both MSM and MSW had non-gonococcal, non-chlamydial urethritis, which suggests the need for improved diagnostic testing.

KEYWORDS: urethritis, men who have sex with men, sexually transmitted diseases

INTRODUCTION

Urethritis is a disease characterized by urethral inflammation and is a common presentation of several sexually transmitted infections (STI). Symptoms of urethritis include discharge, dysuria, urinary frequency, pruritus and/or irritation with micturition. The most common infectious etiologies of urethritis are gonorrhea and chlamydia [1]. These two STIs account for a significant burden of disease in younger individuals with over 1.4 million cases of chlamydia and 300,000 cases of gonorrhea reported in the United States (US) in 2013 [1]. Other causes of urethritis include different bacterial pathogens, viral pathogens, parasitic pathogens and non-infectious causes [2-4]. A significant number of urethritis cases are often due to non-gonorrheal, non-chlamydial (NGNC) infections [5, 6]. The etiology of urethritis may also differ by sexual behavior [7, 8]. Men who have sex with men (MSM) are a group disproportionately affected by HIV and other STIs [9, 10]. Men who specifically have anal sex with other men may be at risk of other urogenital pathogens that could potentially cause urethritis other than gonorrhea and chlamydia [10]. It is the goal of this study to determine if the etiologies of urethritis according to different sexual behaviors are likely to predict the incidence of NGNC infections.

MATERIALS AND METHODS

Study Sample

A retrospective study was performed on all men presenting to the only publicly funded STI Clinic at The Immunology Center at The Miriam Hospital in Providence, Rhode Island (RI) from January 2012 to May 2014. Upon presentation to the clinic, all individuals complete a one-page assessment of demographics and behaviors used for surveillance and reporting purposes. Behavioral questions included number of sex partners in the past 12 months (oral, vaginal, and anal sex), number of HIV positive partners, number of partners with condomless sex, number of partners who were intravenous drug users (IDU), history of a prior STI, and anonymous partners. Men that had sex with men only and men that had sex with men and women were considered as MSM. Men who had sex with only women were considered MSW. All patients submitted first-void urine specimens for the purpose of *N. gonorrhoeae* and *C. trachomatis* testing via nucleic acid amplification tests (NAAT) using the Hologic Gen-Probe TIGRIS, APTIMA assay®.

Statistical Methods

All analyses were conducted using SAS Software 9.4. Predictors of interest for gonorrhea and chlamydia status were modeled using a generalized model assuming a binary distribution with sandwich estimation. Predictors of interest include sexual behavior (MSM/MSW), number of sexual partners in the last year, history of STI in last year and in lifetime, and presence/absence of urethritis symptoms of dysuria and discharge. When no significant interaction between the predictors of interest was found, the results for each group were examined. Differences between groups were assessed using a two-sample proportions test and independent sample t-tests. Alpha was set *a priori* at 0.05 level and all confidence intervals are set at the 95% level.

RESULTS

During the study period a total of 1081 male patients presented for STI testing. The geographic distribution of patients included Rhode Island 92%, Massachusetts 5%, Connecticut 1%, and other 2%. The median age was 30 years (range 15-74 years, SD 11.6, inter-quartile range (IQR) 15). The distribution of race included White/Caucasian 69%, Black/African American 20%, Asian 3%, and other 7%. Hispanic/Latino patients comprised 22% of the population. In terms of sexual behavior, 39% (423/1081) of patients identified as being MSM, 59% (643/1081) of patients identified as being MSW and 1% (13/1081) of patients identified with other sexual behaviors or their behaviors were unknown. The average and median numbers of sexual partners in the overall sample were 5.2 and 3.0 partners (SD 7.1, IQR 4), respectively. Of all patients tested, 3% (31/1081) tested positive for gonorrhea, 9% (102/1081) patients tested positive for chlamydia, and 1% (7/1081) tested positive for both. Patients who were symptomatic with urethritis comprised 11% (119/1081) of the sample. Patients who comprised the 962 not meeting the criteria for urethritis were asymptomatic and returning to clinic for concern of subclinical infection, or had symptoms that were not related to urethritis. (**Table 1**)

Behavior as a predictor of STI, with and without urethritis

The odds of gonorrhea were 9.4 times (95% CI [4.4, 20.1]) higher for those with urethritis compared with those without urethritis, p<0.01. Of those with urethritis, the odds of gonorrhea were 4.9 (95% CI [1.5, 15.8]) times higher for MSM compared with MSW, p<0.01. Of those without urethritis, the odds of gonorrhea were not significantly different, p=0.20.

In addition, the odds of chlamydia were 4.6 (95% CI [2.8, 7.4]) times higher for those with urethritis compared with those without urethritis, p<0.01. Interestingly, of those with urethritis, the odds of chlamydia were not significantly different for different sexual behaviors, p=0.23.

In addition to sexual partner preference, lifetime and recent STI history and number of sexual partners were also examined. Of those with urethritis, lifetime history of STI was not predictive of gonorrhea, p=0.65, though the odds of gonorrhea were 3.6 times (95% CI [1.1, 12.4]) higher for those with a 12 month history of an STI compared to those without this history, p=0.04. Number of partners in the last 12 months was not predictive of gonorrhea, p=0.10 or chlamydia, p=0.41.

Table 1. Men with Symptomatic Urethritis

	MSM (N=40)	MSF (N=79)	P value (0.094)
Age			
Average	34 ±12.2	32 ±10.1	0.344
Range	16-31	16-58	
Race			
Asian	5% (2)	3% (2)	1.000
Black or African American	23% (9)	27% (21)	0.663
White/Caucasian	64.3% (26)	57% (45)	0.435
Other	8% (3)	5% (4)	0.686
Ethnicity			
Hispanic or Latino	3% (1)	27% (21)	0.001
Health Coverage			
Medically Insured	23% (9)	18% (14)	0.624
Self-assessed risk of contracting HIV			
Low	20% (8)	37% (29)	0.093
Medium	28% (11)	10% (8)	0.019
High	8% (3)	3% (2)	0.333
(+) HIV test in the past	25% (10)	1% (1)	<0.001
Sexual Behavior			
100% Condom use for anal/ vaginal sex	10% (4)	25% (20)	0.056
Total sex partners in 12 months	9.4 ±13.2	3.6 ±3.2	<0.001
Partners known to have HIV/ IV Drug use	23% (9)	0% (0)	<0.001
Number of partners with unprotected sex	7.5 ±13.8	2.0 ±2.5	<0.001
STI in past the past 12 months	20% (8)	11% (9)	0.268
Lifetime incidence of an STI	45% (18)	39% (31)	0.561
Injection drug use	10% (4)	1% (1)	0.043
Average days with symptoms before evaluation	17 ±44.9	35 ±77.	
Symptoms			
Dysuria	70% (28)	66% (52)	0.685
Irritative urinary symptoms	1% (2)	15% (12)	0.137
Discharge	50% (20)	46% (36)	0.700
Dyspareunia	0% (0)	3% (2)	0.550
Urinary frequency	8% (3)	4% (3)	0.403
Urine PCR			
(+) Gonorrhea	25% (10)	6% (5)	0.007
(+) Chlamydia	20% (8)	30% (24)	0.277
NGNCU	60% (24)	65% (51)	0.690

MSM, men who have sex with men
MSF, men who have sex with women only
HIV, human immunodeficiency virus
STI, sexually transmitted infection
PCR, polymerase chain reaction (described in methods)
NGNCU, non-gonorrheal non-chlamydial urethritis

Symptoms as a predictor of STI

Of those with urethritis, dysuria was not predictive of chlamydia or gonorrhea, p=0.51 and p=0.27, respectively. Likewise, discharge was not predictive of chlamydia, p=0.23. However, discharge was predictive of gonorrhea, p=0.0047. Specifically, odds of having gonorrhea were 9.2 (95% CI [2.0, 43.0]) times higher for those with discharge compared with those without discharge.

DISCUSSION

Urethritis is a common male presentation to clinics which specialize in STIs or men's health. By identifying sexual behaviors, clinicians may be able to provide counseling as well as aid in the diagnostic work-up of urethritis, however these findings aid in completing a holistic picture rather than suggest a modification in practice.

Differences in sexual behaviors may contribute to the variety of pathogenic etiologies in men with urethritis. There is evidence to suggest that sexual networks facilitate the spread and persistence of certain STIs [11, 12]. Studies show that MSM have higher rates of gonorrhea in general [13]. The results of this study further corroborate these numbers and demonstrate that MSM with urethritis have four times the odds of gonorrhea compared with MSW. Differences in anal flora compared to vaginal flora may predispose or facilitate development of different pathogens compared to MSW, however more research is necessary regarding this theory [13]. This theory may spur further motivation for diagnostic evaluation of extragenital sites, such as rectal NAAT for known STI [14].

Despite *neisseria gonorrhoeae* and c*hlamydia trachomatis* being the most common causes of urethritis in men, we found a significant number of NGNC cases [2, 15]. This can present a significant challenge for medical providers and specialists. Patients diagnosed with NGNC urethritis oftentimes present to urologists, and without a high degree of suspicion for other pathogens, a potential curable etiology may be missed. Using highly sensitive conventional diagnostic testing, detection rates of gonorrhea in symptomatic patients are approximately 20% while rates of chlamydia range from 15-30% [18]. Given this study and existing literature, it is important to consider alternative diagnostic tests, which further characterize urethritis. In some men, no etiology of urethritis can be found despite intensive work-up.

Understanding the wide range of differences in behaviors and lifestyles of patients is important to identify potential etiologies of urethritis and other diseases. This study further demonstrates that there are, in fact, significant behavioral differences between MSM and MSW in terms of number of sexual partners and condomless sex. It is clear from the literature that high-risk sexual behaviors and lifestyles predispose patients to repeat STI, HIV, and other poor health outcomes [19]. Counseling and education would benefit men with urethritis and risk regarding HIV acquisition; all men who present with urethritis or are diagnosed with an STI should be screened for HIV [20].

Limitations

Although this study used a consistent definition of urethritis by utilizing symptomatic measures, objective measures were not used (WBC on urethral swab, first-void urine, or discharge on physical exam). Distinguishing between UTI and urethritis without a urine analysis, urethral smears, or urine cultures may have led to inappropriate characterization as urethritis. The retrospective nature of the study also limited associations that could be made between the outcomes of interest and demographic and behavioral data. In addition, a selection bias may exist for our data, given that patients presented to an STI clinic, instead of their primary care physician or urologist; thus our scope of inference is limited to those presenting to an STI clinic.

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Clinical presentation, pathophysiology, diagnosis, and treatment of acquired and hereditary angioedema: Exploring state-of-the-art therapies in RI

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ABSTRACT

Hereditary and acquired angioedema are potentially life-threatening diseases characterized by spontaneous episodes of subcutaneous and submucosal swelling of face, lips, oral cavity, larynx, and GI tract. Hereditary angioedema (HAE) usually presents within the first and second decades of life, whereas acquired angioedema presents in adults after 40 years of age. These clinical symptoms together with reduced C1 inhibitor levels and/or activity can usually confirm the diagnosis. In recent years, multiple novel therapies for treating hereditary angioedema have emerged including C1 inhibitor concentrates, ecallantide/kallikrein inhibitor, and icatibant/bradykinin receptor antagonist. This article reviews the clinical presentation, diagnosis, treatment, and prophylaxis of HAE. Lastly, this article takes into consideration that, in reality, acute care treatment can often be limited by each hospital's formulary, included is a review of HAE treatments available at the nine major hospitals in Rhode Island.

KEYWORDS: hereditary angioedema, acquired angioedema, Rhode Island, C1-INH

INTRODUCTION

Hereditary and acquired angioedema are conditions characterized by acute swelling of the subcutaneous and submucosal tissues, which can progress to involve more surface areas or threaten life when it involves the laryngeal tissue. In addition to causing significant mortality and morbidity, HAE attacks are also associated with significant loss of school/work days and reduction in quality of life. Hereditary angioedema (HAE) is an autosomal dominant condition which occurs in about 1:10,000 to 1:50,000 in the general population [1]. Acquired angioedema (AAE) occurs in about 1:100,000 to 1:500,000 in the general population [2]. Given that the population of Rhode Island (RI) is estimated to be about 1 million people [3], this extrapolates to a prevalence of 20–100 patients with HAE and 2–10 patients with AAE in RI.

Fortunately, novel targeted therapies for acute HAE exacerbations have emerged in the last 7 years. This article reviews the clinical presentation, diagnosis, prophylaxis and treatment of attacks. Also included is a review of currently available HAE treatments at the nine major hospitals in RI because, in reality, acute care treatment in the emergency department (ED) is often limited by a local hospital's formulary.

This is a qualitative and not a systematic review of the treatment of HAE, and by extension, AAE.

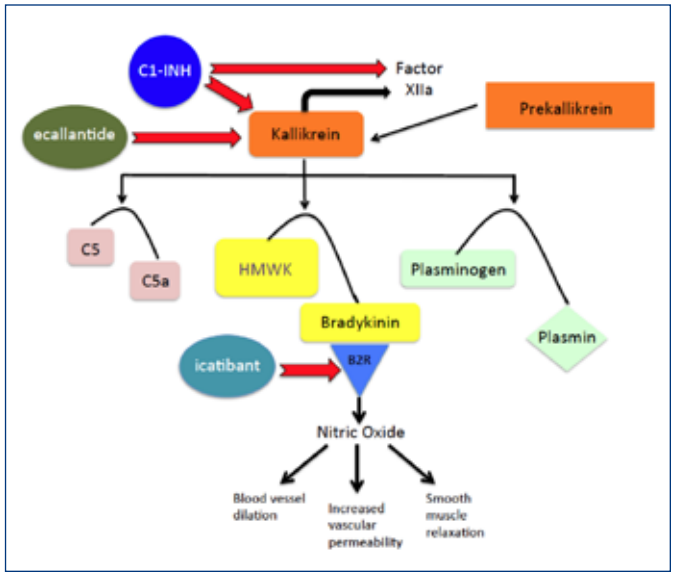
CLINICAL PRESENTATION

Patients with HAE and AAE experience recurrent episodes of submucosal and subcutaneous edema involving the face, tongue, GI tract, or larynx, which may be life threatening. The severity and frequency of acute attacks of angioedema are variable, ranging from once/year to three attacks/week [4]. HAE usually first clinically presents in the 1st and 2nd decades of life, whereas AAE usually presents after 40 years of age [2]. AAE is frequently due to an underlying lymphoproliferative or autoimmune disorder [5].

PATHOPHYSIOLOGY

The underlying pathophysiology of angioedema involves the activation of the kallikrein-kinin cascade. C1-INH directly inhibits both kallikrein and Factor XIIa, the latter of which catalyzes the formation of kallikrein (**Figure 1**). Once formed, kallikrein converts high molecular weight kininogen (HMWK) into bradykinin, which activates its receptor B2R

Figure 1. Kallikrein-kinin cascade and targeted therapeutic interventions.



to stimulate nitric oxide release, blood vessel dilation, and increased vascular permeability, resulting in angioedema.

DIAGNOSIS

Although this article focuses on HAE and AAE, it is important to appreciate that these diseases are amongst the least common causes of angioedema that present to the ED. Angioedema accounts for about 100,000 visits to the ED each year [6]. The most common cause of angioedema (severe enough to warrant an ED visit) is ACE-inhibitor induced angioedema, accounting for 20-40% of ED presentations [7, 8]. Another common culprit for angioedema is nonsteroidal anti-inflammatory drug (NSAID)-induced angioedema accounting for 11% of cases [9, 10]. Often, however, the cause is never identified; these idiopathic cases are referred to and further subdivided into histaminergic and nonhistaminergic variants.

There are three types of HAE. Type I is characterized by a quantitative decrease in C1-INH level (majority of cases); Type II, by a reduction in functional C1-INH activity; and Type III, by normal C1-INH level and activity (rare). Type III patients are almost exclusively female and have a positive family history or Factor XII mutation or defects in bradykinin metabolism (**Table 1**).

Table 1. Differentiating laboratory findings in acquired angioedema and hereditary angioedema. Red arrows indicate decreased level or function; blue arrows indicated increased level or function.

		C1-INH level	C1-INH activity	C1q	C4	C1-INH Ab
HAE	Type I	↓	↓	normal	↓	none
	Type II	normal or ↑	↓	normal	↓	none
	Type III	normal	normal	normal	normal	none
AAE	Type I	↓	↓	↓	↓	none
	Type II	normal or ↓	↓	↓	↓	↑

Diagnosis may be made in the appropriate clinical setting by obtaining two separate serologic measurements demonstrating decreased C4 levels and C1-INH antigen or function 1-3 months apart [2]. Decreased C4 levels and C1-INH antigen or function also characterize AAE. Measurement of C1q is useful to distinguish HAE from AAE; it is normal in HAE, but low in AAE [11]. There are two types of AAE. Type I occurs when immune complexes consume C1-INH; Type II, when anti-C1-INH antibody neutralizes C1-INH (**Table 1**) [12].

HAE has been associated with mutations in the SERPING1 gene [2]. Genetic testing should be considered when clinical and laboratory data are insufficient for diagnosis. Patients diagnosed with AAE should undergo work-up for underlying lymphoproliferative and autoimmune disease [5, 11].

TREATMENT OF ACUTE ATTACKS

The recommendation from the international allergy/immunology and emergency medicine community is to treat acute attacks of hereditary angioedema because the consensus is that treating acute attacks will reduce mortality [2, 13-15]. Though the literature lacks a study that randomizes patients to treatment or placebo to specifically examine mortality – a study unlikely to be approved by an IRB – there is a study that examined 70 patients of whom asphyxiated from a laryngeal attack, 63 (90%) of those were undiagnosed [16]. Undiagnosed patients often receive inappropriate therapy (including surgery) or delay in emergency treatment [16-18]. Lastly, there's no evidence that treating acute attacks of hereditary angioedema increases mortality. Given the efficacy, safety profile, and risk of withholding treatment, the international allergy/immunology and emergency medicine community recommends administering therapies during an acute attack [2, 13-15].

The major goals of treating acute attacks are to avoid asphyxiation and provide symptomatic relief. Mechanistically, treatments should halt or dampen activation of kallikrein-kinin cascade (**Figure 1**). Therapies target crucial points in the pathway. C1-INH is a serine protease that directly inhibits kallikrein and factor XIIa. Two brands of C1-INH are currently FDA approved for acute attacks of HAE; Berinert® (CSL Behring, King of Prussia, PA) is the human plasma derived C1-INH and Ruconest® (Salix, Raleigh, NC) is a recombinant C1-INH derived from New Zealand white rabbit oocytes. Other FDA-approved treatments for acute attacks include the kallikren inhibitor, ecallantide/Kalbitor® (Dyax, Burlington, MA) and bradykinin receptor antagonist, icatibant/Firazyr® (Shire, Lexington, MA).

Currently there are no FDA-approved therapies for AAE. Management of AAE focuses on treating the underlying condition. Additionally, it is commonplace in medical practice to make off-label use of the above HAE products for the treatment of acute AAE attacks. However the evidence for this utilization is limited to case reports [19, 20].

In clinical practice, acute care treatment in the ED is often limited by local hospital formulary. In Rhode Island, of the nine major hospitals with emergency departments, only five carry treatment for acute HAE attacks on their formularies at the current time (**Table 2**). This information is important to consider when referring HAE/AAE patients for ED care.

Berinert®

Ten studies have been performed, involving 537 subjects. One randomized controlled trial showed that treated subjects had a statistically significant benefit in time to relief and time to complete resolution, as compared with placebo treatment, and with a lower adverse event profile. Currently Berinert is FDA approved for on demand self-administration of acute attacks and can be administered at home or in the ED.

Table 2. HAE acute treatment availability per local hospital formularies in Rhode Island as of March 10th, 2016.

Hospital	Medication on formulary
Rhode Island Hospital	Berinert
The Miriam Hospital	Berinert
Newport Hospital	Berinert
South County Hospital	Berinert
Westerly Hospital	Kalbitor
Kent Hospital	None
Roger Williams Medical Center	None
Memorial Hospital	None
Landmark Medical Center	None

Ruconest®

Two randomized, placebo controlled trials (RCTs), showed that the median time to start of symptom relief was significantly lower in the Ruconest arm at 100 U/kg (66 vs 495 minutes, *p-value* <0.001), and at 50 U/kg (122 vs 495 minutes, *p-value* 0.013) [22].

An assessment for IgE mediated hypersensitivity to rabbit can be performed prior to administration in patients with suspected rabbit allergy. Appropriately trained patients may self-administer upon recognition of an HAE attack. As such it can be administered at home or in the ED.

Ecallantide/Kalbitor®

Ecallantide is a direct kallikrein inhibitor. The EDEMA 3 and 4 were RCTs designed to evaluate efficacy and safety of ecallantide [23, 24]. EDEMA3 found significantly greater symptom relief compared to placebo (p-value 0.004) [23]. EDEMA4 showed significant improvement of symptoms compared to placebo at 4 hours (*p-value* 0.01) and at 24 hours (*p-value* 0.04) [24]. Adverse events were mildly increased in the treatment arms [23, 24].

It is not approved for self-administration at home because 3% of patients experienced anaphylaxis [1]. In order to heighten awareness of this anaphylaxis risk, the FDA has required that the prescribing information include a black-box warning mandating that only health-care professionals trained in managing anaphylaxis administer this drug. In order to facilitate treatment in patients who may be traveling, the manufacturer has a program, which coordinates the services of a healthcare professional to administer the medication at a medical facility in close proximity to the travel destination.

Icatibant/ Firazyr®

Icatibant (Firazyr) acts through an alternative mechanism to interrupt the kallikrein-kinin pathway by blocking the bradykinin receptor (**Figure 1**). While one RCT failed to show a reduction in time to improvement, another demonstrated that the median time to symptomatic reduction of 50% or more in moderate to very severe acute episodes was achieved in a significantly shorter time in the icatibant group than placebo group (2 vs 19.8 hours, *p-value* <0.001) [26]. Time to complete relief of symptoms was also significant (8.0 vs 36.0 hours, *p-value* <0.001) [26]. Icatibant is FDA approved for subcutaneous self-administration of acute attacks of hereditary angioedema and can be administered in the ED or home setting.

Each of these drugs has FDA approval for treatment during acute attacks. Because there are no trials comparing these therapies to each other, it is left to the medical care professionals to determine the most efficacious and safest treatment option for acute care of each patient. The therapies are summarized in **Table 3**.

Table 3. Comparing and contrasting FDA-approved therapies for acute HAE attacks with respect to relative advantages, mechanism of action, route of administration, half-life, adverse events, and approved indication. *Adverse events occurring at frequency greater than 2% documented in the prescribing information [39-42].

Drug	Advantages	Mechanism of Action	Route of Administration	Half-life (hours)	Adverse Events*	FDA Approval
Berinert®	Long half-life, more likely to avoid re-dose	Replacement with plasma derived C1-INH	IV	22.4 in children, 16.7 in adults	Nausea, dysgeusia, abdominal pain, vomiting	Self-administration in adolescents and adults
Ruconest®	No known risk of human viral transmission	Replacement with recombinant rabbit oocyte derived C1-INH	IV	2.5	Headache, angioedema, vertigo	Self-administration in adolescents and adults
Ecallantide/ Kalbitor®	Subcutaneous administration	Recombinant plasma kallikrein inhibitor	SQ	2	Headache, nausea, diarrhea, pyrexia, injection site reaction, nasopharyngitis	Trained healthcare professional administration for patients >12 years old
Icatibant/Firazyr®	Subcutaneous self-administration.	Bradykinin receptor antagonist	SQ	1.4	Injection site reaction, pyrexia, dizziness, transaminase increase	Self-administration in those >18 years old

PREVENTION

HAE and AAE patients who suffer particularly severe or frequent attacks may receive long-term prophylaxis. It may also be reasonable to administer a short course of prophylaxis prior to dental procedures, surgeries or other events likely to precipitate an attack. Options for prophylaxis include C1-INH concentrate and androgens.

Cinryze® (Shire, Lexington, MA) is a plasma derived C1 inhibitor used for prophylaxis in adults and adolescents. Clinical efficacy was reported in a randomized controlled crossover trial involving 22 patients with HAE [34]. Adverse reactions manifested as pruritis, rash, lightheadedness and fever. (34)

Danazol (an androgen) was first used for HAE in the 1970s and continues to be used today [35]. The exact mechanism is unknown but it is generally accepted that it increases C1-INH concentrations and enhances breakdown of bradykinin. In two RCTs, patients on danazol experienced significantly fewer acute attacks than those on placebo (p-values <0.001 for both studies) [36, 37]. It is generally well tolerated but can have serious side effects: hepatotoxicity, stroke, hypertension, lipid abnormalities, myopathies, abnormal menses, mood disturbances, and a masculinizing affect in females [35]. It is contraindicated in pregnant women and not recommended for use in children because it may result in premature epiphyseal closure.

CONCLUSION

Availability of acute and prophylactic treatments for HAE has expanded in the last 7 years. However there are no trials demonstrating superiority of one treatment over another. As such, it is advised that prescribers create an individualized treatment plan for patients with HAE [38]. Factors to consider while creating an individualized plan include age, gender, frequency and severity of attacks, and preference for home or facility administration. With the right drug and treatment plan, patients have the best opportunity to realize improvement in their quality of life and to avoid life-threatening complications.

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Disclosures

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Use of emerging tobacco products among adolescents who do not smoke conventional cigarettes

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Although youth cigarette smoking has steadily declined across the US, use of emerging tobacco products, most notably e-cigarettes and hookah, has increased.[1] In 2015, 25.3% of US high school youth currently used at least one tobacco product.[1] E-cigarettes were the most commonly used product (16.0%), surpassing all other products including cigarettes (9.3%), cigars (8.6%), hookah (7.2%), and smokeless tobacco (6.0%). From 2011-2015, youth use of e-cigarettes and hookah substantially increased, while use of cigarettes, cigars, and smokeless tobacco declined. Increased use of emerging products has essentially canceled out decreases in cigarette use, resulting in no change in overall tobacco use among youth.[1]

In Rhode Island (RI), current cigarette use among high school students declined from 8.0% in 2013 to 4.8% in 2015 – one of the lowest youth smoking rates in the country. E-cigarette data were collected for the first time on the 2015 RI Youth Risk Behavior Survey (YRBS). Despite the fact that most RI high school students do not smoke conventional cigarettes, 25.1% of all youth reported current use of tobacco (cigarettes, cigars, smokeless, or e-cigarettes) in 2015. E-cigarettes were the most commonly used product (19.3%), followed by hookah (11.8%), cigars (8.4%), smokeless tobacco (5.3%), and cigarettes (4.8%).

Youth use of any tobacco or nicotine product is unsafe. Exposure to nicotine during adolescence can harm brain development and lead to more severe levels of nicotine addiction.[2] Research suggests that e-cigarette use among youth who do not smoke conventional cigarettes may act as a gateway to initiation of combustible tobacco products.[3] Because RI's youth cigarette smoking rate is so low, yet one in four adolescents report using tobacco, it is important to understand what other tobacco products are used by adolescents who are not current cigarette smokers. This study aimed to 1) describe current use of four tobacco products among RI high school youth who do not smoke conventional cigarettes (hereby referred to as "nonsmokers") and 2) identify factors associated with e-cigarette use among nonsmokers.

METHODS

We used data from the 2015 High School RI YRBS. The YRBS is developed by the Centers for Disease Control and Prevention (CDC), and is conducted biennially in US public high schools and middle schools. The YRBS uses a two-stage, cluster sample design to generate a representative sample of students in grades 9–12. Further description of YRBS methodology is described elsewhere.[4]

In 2015, 3,462 public high school students completed self-administered paper surveys. The analytic sample was limited to adolescents who were not current cigarette smokers (n=3,109) defined as reporting *zero* days to the question: "during the past 30 days, how many days did you smoke cigarettes?" Current use (past 30 days) of four emerging tobacco products was calculated for nonsmoking youth: 1) *electronic vapor products* (e-cigarettes, e-cigars, e-pipes, vape pens, e-hookah, and hookah pens); 2) *cigars* (little cigars and cigarillos); 3) *smokeless tobacco* (chewing tobacco, snuff, and dip); and 4) *hookah* (defined as a large water pipe to smoke tobacco/shisha). Prevalence of each product was cross-tabulated by age, grade, sex, race/ethnicity, sexual orientation, and disability status.

Multivariate logistic regression was used to identify factors associated with e-cigarette use among nonsmokers. The outcome variable was current e-cigarette use defined as past 30-day use of an electronic vapor product. Covariates were demographic characteristics (age, grade, gender, sexual orientation), disability status (physical or emotional/learning), current alcohol use (any use past 30 days), current marijuana use (any use past 30 days), and other tobacco products (smokeless tobacco, hookah, or cigars). Adjusted odds ratios with 95% confidence intervals were calculated. Statistical significance for regression coefficients was tested using the Wald chi-square statistic ($p<.05$).

RESULTS

About one in five (20.7%) nonsmoking RI youth reported current use of at least one other tobacco product. E-cigarettes (15.3%) were the most commonly reported product used among nonsmoking youth. Hookah use (9.2%) was the second most commonly used product, followed by cigars (4.4%) and smokeless tobacco (2.3%). Of youth using only one product (12.6%), the most commonly used product was e-cigarettes (60.2%), followed by hookah (26.8%). Among adolescents using ≥2 products (8.2%), e-cigarettes (95.3%) were most common, followed by hookah (72.4%). Product type prevalence by participant characteristics is presented in Table 1. Emerging product use was generally more frequent among youth who are male, non-Hispanic White, older, sexual miniorities, or youth with a disability.

Table 1. Characteristics of adolescents who do not smoke conventional cigarettes by current use of emerging tobacco products

Characteristics	E-cigarettes % (95% CI)	Smokeless tobacco products % (95% CI)	Hookah % (95% CI)	Cigars, cigarillos, little cigars % (95% CI)
Overall	15.3 (12.0 – 18.5)	2.3 (1.2 – 3.4)	9.2 (7.0 – 11.5)	4.4 (3.2 – 5.6)
Age				
< 15 years	10.7 (7.0 - 14.3)	1.7 (0.6 - 2.6)	6.0 (4.8 – 7.2)	2.4 (1.8 – 3.0)
16 to 18 years	17.7 (13.9 - 21.6)	2.7 (1.4 – 4.0)	11.0 (7.9 – 14.1)	5.5 (3.9 – 7.2)
Sex				
Female	14.0 (10.9 – 17.2)	--	10.6 (7.2 – 14.1)	1.7 (0.9 – 2.5)
Male	16.5 (11.9 – 21.0)	3.8 (2.1 – 5.5)	7.8 (6.0 – 9.7)	7.1 (5.1 – 9.2)
Sexual orientation				
Gay/Lesbian/Bisexual	19.9 (13.5 – 26.3)	--	13.2 (5.9 – 20.5)	--
Heterosexual	15.0 (11.1 – 18.9)	2.4 (1.2 – 3.5)	8.7 (6.4 – 10.9)	4.5 (3.1 – 5.9)
Race/ethnicity				
Hispanic	12.9 (8.9 – 16.9)	--	12.4 (8.2 – 16.7)	3.3 (1.2 – 5.3)
Non-Hispanic Black	10.1 (8.4 – 11.9)	--	--	--
Non-Hispanic White	17.3 (12.5 – 22.1)	2.6 (1.4 – 3.8)	8.7 (6.2 – 11.3)	5.2 (3.6 – 6.8)
Non-Hispanic other race groups	11.6 (7.2 – 16.1)	--	8.2 (3.7 – 12.7)	--
Grade				
9th	11.1 (7.3 – 15.1)	--	6.4 (3.5 – 9.3)	2.0 (0.8 – 3.2)
10th	16.6 (11.7 – 21.5)	2.6 (0.8 – 4.3)	9.6 (5.9 – 13.2)	4.5 (2.7 – 6.4)
11th	12.5 (10.1 – 14.8)	--	9.5 (4.8 – 14.1)	3.7 (1.3 – 6.1)
12th	21.8 (14.7 – 28.9)	--	11.7 (8.8 – 14.5)	7.7 (5.3 – 10.1)
Disability				
No	13.5 (10.3 – 16.7)	2.0 (1.2 – 2.9)	8.4 (6.4 – 10.3)	4.6 (3.2 – 6.2)
Yes	22.9 (16.6 – 29.1)	--	12.8 (7.4 – 18.2)	3.4 (1.7 – 5.1)

-- Unweighted number < = 20
CI = confidence intervals

Regression results (Table 2) showed the odds of e-cigarette use were significantly associated with being male (aOR=1.47, 95% CI=1.02-2.11, p=.04), having a disability (aOR=1.90, 95% CI=1.28-2.82, p=<.01), current alcohol use (aOR=2.05, 95% CI=1.14-3.68, p=.02), and current marijuana use (aOR=3.23, 95% CI=1.78-5.86, p=<.001). Concurrent use of hookah was strongly associated with e-cigarette use (aOR=10.94, 95% CI=7.3-15.90, p=<.0001) and use of cigars was also significantly associated with e-cigarette use (aOR=4.15, 95% CI=2.07-8.29, p=<.0001). Hispanic, non-Hispanic Black, and non-Hispanic other race groups were significantly less likely to use e-cigarettes compared to non-Hispanic White peers. Age, grade, and sexual orientation were not significant multivariate predictors (p>.05)

DISCUSSION

Preventing youth initiation of tobacco use is a primary goal of CDC and state-based tobacco control programs. In RI, youth use of emerging tobacco products exceeds their use of conventional cigarettes. Recent shifts in youth tobacco use suggest that tobacco control programs should increase surveillance of emerging tobacco products, especially e-cigarettes, to better understand tobacco behaviors among youth who are not conventional smokers. We found that one-fifth of nonsmoking youth reported using at least one other tobacco product. Overall tobacco use among nonsmoking youth was found to be driven mostly by e-cigarettes, followed by hookah use.

Studies have found that nonsmoking youth who used e-cigarettes were more likely to report initiation of combustible products,[3] and were more likely to report intentions to smoke in the near future.[5,6] Adolescents may believe e-cigarettes are less harmful, less addictive than conventional cigarettes, and helpful for quitting.[7] In this study, e-cigarette use was more likely among boys, non-Hispanic White youth, and youth with a disability. E-cigarette use was also associated with other risk behaviors including alcohol and marijuana use. Multiple risk behaviors can be partially explained by adolescent propensity for risk taking and other developmental factors. Findings underscore the importance of substance use interventions that simultaneously target multiple risk behaviors that cluster together.

Regression results showed that hookah use was the strongest predictor of e-cigarette use, followed by cigars. Concurrent use of hookah or cigars raises concerns about the prevalence of multiple product use among youth. Youth that use more than one tobacco product increase their exposure to nicotine and are at higher risk for nicotine addiction. Some nonsmoking youth in RI reported use of two or more tobacco products. Of nonsmoking youth who used an emerging tobacco product, approximately 39% used ≥2 more products. Polytobacco use among youth highlights the variety of tobacco products available to youth, as well as the effect of tobacco industry marketing on youth. Emerging products are commonly available in candy and fruit flavors that appeal to youth. These products are often priced cheaply and marketed to youth in retail environments.

Table 2. Predictors of current e-cigarette use among adolescents who do not smoke conventional cigarettes

Characteristics	Adjusted Odds Ratio	95% CI	P- value
Age			
16 to 18 years	1.07	0.73 – 1.57	0.72
Sex			
Male	1.47	1.02 – 2.11	0.04
Sexual orientation			
Gay/Lesbian/Bisexual	1.48	0.76 – 2.88	0.25
Race/ethnicity			
Hispanic	0.56	0.33 – 0.94	0.03
Non-Hispanic Black	0.35	0.19 – 0.63	<.001
Non-Hispanic other race groups	0.46	0.24 – 0.91	0.02
Disability			
Yes	1.90	1.28 – 2.82	<.01
Current tobacco use			
Use smokeless tobacco products	1.79	0.41 – 7.82	0.43
Use hookah to smoke tobacco	10.94	7.53 – 15.90	<.0001
Smoke cigars, cigarillos, little cigars	4.15	2.07 – 8.29	<.0001
Current alcohol use			
Yes	2.05	1.14 – 3.68	0.02
Current marijuana use			
Yes	3.23	1.78 – 5.86	<.001

Reference groups: Age: 12 to 15 years; Sex: female; Sexual orientation: heterosexual; Race/ethnicity: non-Hispanic white; disability: no; Current tobacco use: none; Current alcohol use: no; Current marijuana use: no; CI = confidence intervals

Findings are subject to at least three limitations. Causality cannot be determined from cross-sectional data. Missing responses may have resulted in underestimation of use of emerging tobacco products. Finally, the YRBS is limited to public school students and may not be generalizable to high school students that attend private schools.

Youth use of emerging products is on the rise. Strengthening policies that reduce youth access to all tobacco products, not just cigarettes, is an effective strategy to prevent youth tobacco use.[8] Best practice and emerging policy initiatives include raising the cost of all tobacco products, raising the minimum age of sale to 21, and creating tobacco-free environments for schools and campuses (inclusive of e-cigarettes). RI already has strong tobacco control policies. RI has the second highest state cigarette tax ($3.75/pack), a comprehensive indoor smoking ban prohibiting combustible products including hookah, and a state law prohibiting e-cigarette sales to individuals under 18. Despite major tobacco control successes, new initiatives are needed to respond to youth uptake of emerging products. Future directions for RI include increased surveillance of emerging products, counter-marketing about the dangers of emerging products, and local point of sale strategies that require local tobacco retailer licenses and ban sales of flavored and discounted tobacco products.

Acknowledgment

We thank the Rhode Island Department of Health, Center for Health Data and Analysis for providing 2015 RI YRBS data.

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Authors

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Rhode Island Monthly Vital Statistics Report
Provisional Occurrence Data from the Division of Vital Records

VITAL EVENTS	REPORTING PERIOD		
	DECEMBER 2015	12 MONTHS ENDING WITH DECEMBER 2015	
	Number	Number	Rates
Live Births	894	11,568	11.0*
Deaths	845	11,380	9.8*
Infant Deaths	1	71	6.1#
Neonatal Deaths	0	57	4.9#
Marriages	361	6,607	6.3*
Divorces	308	3,162	3.0*
Induced Terminations	169	2,528	218.5#
Spontaneous Fetal Deaths	67	604	52.2#
Under 20 weeks gestation	64	558	53.8#
20+ weeks gestation	3	46	4.0#

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

Underlying Cause of Death Category	REPORTING PERIOD			
	JUNE 2015	12 MONTHS ENDING WITH JUNE 2015		
	Number (a)	Number (a)	Rates (b)	YPLL (c)
Diseases of the Heart	168	2,361	223.8	3,334.5
Malignant Neoplasms	200	2,227	211.1	5,204.5
Cerebrovascular Disease	32	432	40.9	535.0
Injuries (Accident/Suicide/Homicide)	71	836	79.2	12,706.0
COPD	47	555	52.6	615.

(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 1,055,173 (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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Working for You: RIMS advocacy activities

May 2, Monday

Meeting with Blue Cross Blue Shield of RI: President Russell Settipane, MD; President-elect Sarah Fessler, MD; and staff

Interview with Providence Business News reporter regarding "Choosing Wisely"

RIMS Board of Directors Meeting

May 3, Tuesday

RIMS Physician Health Committee: Herbert Rakatansky, MD, Chair

Meeting with Department of Health Diabetes Prevention staff

Legislative hearings

May 4, 2016, Wednesday

Legislative hearings

Warren Alpert medical student members Meet-and-Greet with legislators

Chairman Abney fundraiser

Representative Fogarty fundraiser

May 5, Thursday

AMA conference call: MACRA update

Legislative hearings

Massachusetts Medical Society annual meeting

May 9, Monday

Senator Lombardi fundraiser

May 10, Tuesday

American Academy of Family Physicians lobbying day: Steven R. DeToy, Director of Government and Public Affairs, presenter

DOH Health Services Council

Legislative Hearings

May 11, Wednesday

Board of Medical Licensure and Discipline

Governor's Opioid Taskforce: Gary Bubly, MD, Past President, Taskforce member

Legislative Hearings

Senator Goodwin fundraiser

May 12, Thursday

Legislative Hearings

SIM Steering Committee: Peter A. Hollmann, MD

May 16, Monday

Senator Satchell fundraiser

On April 30, RIMS sponsored the Eleventh Hour Education Event, two hours of required CME on Pain Management, Risk Management, and End of Life/Palliative Care in one event. Shown left to right: panelists John Femino, MD; Gary Bubly, MD; James V. MacDonald, MD; and RIMS President Russell A. Settipane, MD

May 17, Tuesday

OHIC Health Insurance Advisory Committee meeting

Legislative hearings

Representative Marcello fundraiser

Representative Hull fundraiser

May 18, Wednesday

DOH Primary Care Physician Advisory Committee

DOH Health Professionals Loan Repayment Awards, Governor's State Room: Steven R. DeToy, Director of Government and Public Affairs, Selection Committee member.

Legislative hearings

Membership Committee: Elaine Jones, MD, and Diane Siedlecki, MD, Co-chairs

Senator Crowley fundraiser

Representative Jacquard fundraiser

May 19, Thursday

Legislative hearings

Representative Ajello fundraiser

Representative Tanzi fundraiser

Senator Goldin fundraiser

May 20, Friday

Diabetes prevention planning with Department of Health and Healthcentric Advisors

May 20–21, Friday–Saturday

New England Delegation to the AMA and Council of New England State Medical Societies, Freeport, Maine: Alyn Adrain, MD, and RIMS staff

May 24, Tuesday

Legislative hearings

EOHHS Provider Advisory Group, hosted by RIMS

May 25, Wednesday

Legislative hearings

Chairman McCaffrey fundraiser

May 26, Thursday

Legislative hearings

May 27, Friday

Presentation of two RIMS awards to graduating medical students, Alpert Medical School, presenter Russell Settipane, MD, President. Amos Throop Prize presented to Haiyan Ramirez Batlle, MD; Herbert Rakatansky Prize presented to Lianna Karp, MD

May 30, Monday

Closed in Observance of Memorial Day

May 31, Tuesday

Legislative hearings

RIMS CORPORATE AFFILIATES

www.carenewengland.org

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.

www.claflin.com

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john@insurehealthgroup.com

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.

www.nhpri.org

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.

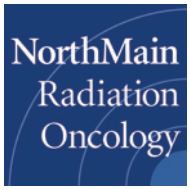
www.ripcpc.com

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



For more information about group rates, please contact Megan Turcotte, RIMS Director of Member Services

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Women & Infants, Bradley Receive $1.5M to Support Phase II of Rhode Island Consortium For Autism Research and Treatment

Grant will enable further recruitment and development of statewide partnership to support population-based research on autism spectrum disorder

The Rhode Island Consortium for Autism Research and Treatment (RI-CART), a group of the state's leading experts on autism research, education, health and services, has received a $1.5 million renewal grant from the Simons Foundation Autism Research Initiative. The three-year grant, awarded to Women & Infants Hospital of Rhode Island, and with a subcontract to Bradley Hospital, will enable RI-CART to continue recruitment and development of a statewide, population-based autism patient registry.

The first grant from Simons Foundation was received in August 2013. Since then, RI-CART has recruited more than 1,000 individuals and their families to participate in the registry. The goal for phase II of this effort is to recruit an additional 1,000 participants into a study that includes a brief clinical assessment, collection of biological samples for genetic analysis, and referrals to other research studies. Participants' families are active in the management and function of RI-CART. The long-term goal is to enroll all individuals with autism in Rhode Island in this unique research network.

"Autism is a poorly understood family of related conditions. Unfortunately, there is no specific medical treatment for autism, underscoring the importance for additional research," said **STEPHEN SHEINKOPF, PhD**, a clinical researcher at Women & Infants Hospital's Brown Center for the Study of Children at Risk, assistant professor at The Warren Alpert Medical School of Brown University, and co-director and principal investigator of RI-CART. "What makes RI-CART truly unique is that this statewide collaboration is building an infrastructure for clinical and translational research on autism spectrum disorders."

A unique aspect of RI-CART is that families actively participate in the management and function of the project. RI-CART has partnered with The Autism Project, an organization that offers support and programming for individuals with autism. "RI-CART is an exciting opportunity for collaboration between clinicians and researchers, as well as the individuals and families impacted by autism," said Joanne Quinn, executive director of The Autism Project and a member of the RI-CART leadership team.

RI-CART has also been supported by funds from the Brown University Institute for Brain Science, the Norman Prince Neuroscience Institute, and the Department of Psychiatry and Human Behavior at The Warren Alpert Medical School of Brown University.

For more information about RI-CART, visit www.AutismRI.org.

About RI-CART

The Rhode Island Consortium for Autism Research and Treatment (RI-CART) is comprised of clinicians, researchers and community members with the shared mission of accelerating research on the causes of and treatments for Autism Spectrum Disorders. RI-CART is a unique collaboration among partner organizations across Rhode Island – the state's leading hospitals including Bradley Hospital, Hasbro Children's Hospital, Women & Infants Hospital, Butler Hospital, Memorial Hospital and Rhode Island Hospital; institutions of higher education including Brown University, the University of Rhode Island and Rhode Island College; service agencies including the Groden Center and Perspectives Corporation; state agencies including the Rhode Island departments of Health and Education; and community programs and parent advocacy groups including The Autism Project. RI-CART is based at Bradley Hospital in East Providence, RI. Learn more by contacting RICART@lifespan.org or on the web at www.AutismRI.org. ❖

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Southcoast Health, Care New England Move to Next Step in Affiliation Process

Combined system would create two-state, eight-hospital, $2 billion-plus, not-for-profit healthcare system

In separate actions undertaken by their respective governance Boards, Southcoast Health and Care New England have voted to move forward with the proposed affiliation of the two not-for-profit hospital and healthcare systems. The announcement was made May 3, 2016 by **CHARLES R. REPPUCCI**, Board Chair for Care New England, and **JEAN F. MACCORMACK**, Board Chair for Southcoast Health.

The two Chairs stated that Southcoast Health and Care New England have worked toward this agreement to affiliate since they announced their intent to study partnership potentials last November. The parties will now move toward the execution of the affiliation agreement and subsequent initiation of the required regulatory review processes in Massachusetts and Rhode Island. Both organizations will continue their collaborative due diligence reviews, and begin to develop the plans to operate an integrated health system capitalizing on each organization's strengths in patient services and population health management.

Combined, the new system would be a $2 billion-plus entity with eight hospitals and more than 15,000 employees. It would span a broad geographic area in Southeastern New England and offer an integrated network of comprehensive patient services.

Care New England and Southcoast Health would be combined under a new system parent entity to be named following a comprehensive brand assessment. The combined not-for-profit system will uphold Care New England's and Southcoast Health's proud traditions of providing the best community-based healthcare possible to all patients.

Under the proposed framework for the new entity agreed upon by each Board, Southcoast Health President and CEO **KEITH HOVAN** will serve as the President and CEO of the new health system parent company; Care New England CEO **DENNIS KEEFE** will become CEO of the Population Health initiative for the unified system; Care New England's Board will select the new Chair of the system parent Board, and the Southcoast Health Board Vice Chair will serve as its Vice Chair. Southcoast Health and Care New England will each select 10 individuals in all to serve on the new system parent Board of Trustees.

The Population Health initiative will be a signature program for the new system. Both Care New England and Southcoast Health have established Accountable Care Organizations and have been working to advance innovative approaches to care that improve outcomes, enhance patient experience and reduce cost.

"We know nothing is more important to the people of southeastern Massachusetts and Rhode Island than a strong future for the healthcare systems that safeguard their health while providing jobs and community benefits, and advancing our teaching and research missions," said Reppucci.

"This affiliation helps to build an even stronger future for our organizations while importantly maintaining our steadfast commitment to our local communities. We look forward to continuing this collaborative and transparent process, sharing additional details about our vision for healthcare delivery as plans are developed and as we begin the regulatory process," said MacCormack. ❖

Roger Williams' gastroenterologist introduces new stent technology

PROVIDENCE – **DR. NABIL TOUBIA** is the first physician in Rhode Island to utilize new stent technology that helps physicians manage serious complications from pancreatitis using a minimally invasive endoscopic approach. On April 28, Dr. Toubia, a gastroenterologist at Roger Williams Medical Center, utilized the new AXIOS stent technology on a patient's pancreas, while guided by ultrasound.

This technology has been FDA-approved and on the market since March 2016. The AXIOS System, a product of the Boston Scientific Corporation, has been cleared for endoscopic management of pancreatic pseudocysts and certain types of walled-off pancreatic necrosis.

"This technique for treating pancreatic pseudocysts is not new; the technology, however, is," said Dr. Toubia. "We can now treat certain complications in the pancreas in a safer, less invasive manner and that is good news for our patients."

This system is the first stent specifically designed for drainage of a pancreatic pseudocyst by creating a new, temporary opening between the pancreas and the gastrointestinal tract. The new technology enables physicians like Dr. Toubia to complete this procedure with just one stent, as opposed to the previous technique. This advancement allows for reduced procedural time with less manipulation and less complication. ❖

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Southcoast Health expands existing relationship with Boston Children's Hospital; physician leadership appointed

NEW BEDFORD, MASS.—SouthcoastHealth has expanded its affiliation with Boston Children's Hospital to include the Level II nurseries at Charlton Memorial Hospital in Fall River and St. Luke's Hospital in New Bedford as of May 1.

Southcoast Health currently has an affiliation with Boston Children's for pediatric inpatient and emergency care at St. Luke's as well as nursery care at Tobey Hospital in Wareham.

A change in physician leadership will accompany this transition.

BRIAN SARD, MD, has been appointed Chair of Pediatrics. Dr. Sard served as the medical director of pediatric programs at St. Luke's since 2012. Dr. Sard has led the program to significant growth in terms of both patients seen and services provided during his tenure. In his new role, Dr. Sard will oversee delivery of pediatric and newborn care across Southcoast Health, collaborating closely with clinical leadership in neonatology, obstetrics and other departments, as well as administrative leaders at both Southcoast Health and Boston Children's.

ATHENA XIFARAS, MD, will continue to serve as a leader within the pediatric program in her role as Division Chief of Inpatient Pediatrics. This work includes coordinating pediatric care both within the St. Luke's pediatric program and with community providers across Southcoast Health.

DAPHNE REMY GOMES, MD, MPH, will take on the role of Division Chief of Neonatology and Site Leader for the Charlton Memorial Hospital Special Care Nursery. Dr. Gomes has served as a staff neonatologist within level IIA, IIB and III nurseries across the Boston Children's affiliated community hospitals since 2013, currently as an attending neonatologist at Winchester Hospital. Dr. Gomes also spent time as a neonatology consultant in Rwanda and currently serves as the Associate Director of Education for the Boston Children's Division of Newborn Medicine; work that includes facilitation of neonatal simulation training.

JESSICA SLUSARSKI, MD, will be the Site Leader for the St. Luke's Hospital Special Care Nursery. Dr. Slusarski has been part of the team from Women & Infants Hospital of Rhode Island for the past six years. At Women & Infants, she was a leader of the transport team and has experience with simulation training. Dr. Slusarski also served as an Assistant Clinical Professor of Pediatrics at both the University of Washington and more recently at Brown University. For the past three years, Dr. Slusarski has served as the Medical Director of Neonatal Transport for Women & Infants' NICU.

CYNTHIA DE MEESTER, MD, PhD, has been named the Site Leader for the Tobey Hospital Nursery. Dr. De Meester brings more than 15 years of experience from both the pediatric primary care and hospital-based perspective, most recently as a pediatric hospitalist at Cape Cod Hospital. In addition, Dr. De Meester offers program administrative experience and a personal interest in working with families that struggle with addiction. ❖

RI Health Centers Receive Nearly $3M to Expand Services

PROVIDENCE – Rhode Island's Congressional delegation announced on May 6th that three Rhode Island health centers will receive $2,988,180 from the U.S. Department of Health and Human Services (HHS) for facility renovation and expansion, increasing access to health care for a projected 11,250 additional patients.

Comprehensive Community Action in Cranston and Blackstone Valley Community Health Care in Pawtucket will receive $1 million each and the Providence Community Health Centers in Providence will receive $988,180.

"We are extremely excited about receiving this grant, and want to thank our entire federal delegation for their continue support," said Joanne McGunagle, President and CEO, Comprehensive Community Action (CCAP). "This funding will allow CCAP to expand much needed quality and affordable dental services at our Family Health Services of Coventry health center."

"We are most appreciative of the efforts of our Congressional delegation for their continued support of health centers. Our HRSA funding will help Blackstone establish the nation's first Neighborhood Health Station in Central Falls. We look forward to great accomplishments with the help of this federal funding," said Ray Lavoie, Executive Director, Blackstone Valley Community Health Care.

"The Providence Community Health Centers are very happy to receive this grant as it will allow us to add additional exam rooms and clinical support space needed to meet our growing patient's needs. We also thank our entire Rhode Island Congressional delegation as their continued support make grants like this possible, and directly impact our community," said Merrill Thomas, CEO and President, Providence Community Health Centers. ❖

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Appointments

Nitin S. Damle, MD, named President of the American College of Physicians

PHILADELPHIA — **NITIN S. DAMLE, MD, MS, FACP**, has been named President of the American College of Physicians (ACP). ACP is the nation's largest medical specialty organization with 143,000 members. Dr. Damle's term began at the conclusion of the organization's annual scientific meeting, in Washington, DC, from May 5–7, 2016.

Dr. Damle is the founding and managing partner at South County Internal Medicine Inc. in Wakefield, Rhode Island since 1988. He is past President of the Rhode Island Medical Society and past President of the Medical Staff of the South County Hospital Health Care System and a member of the Board of Trustees.

He has been a Fellow (FACP) of the ACP since 1992. Prior to his term as a Regent he was the Governor from the Rhode Island Chapter of the ACP and during his term, was the Vice-chairman of the Education, Quality and Publications Policy Committee. As Governor, he won an ACP Evergreen Award for innovative College Chapter activities.

He was the Chairman of ACP's Medical Practice and Quality Policy Committee for two years and Chairman of ACP Services and ACP Services Political Action Committee, which is the advocacy arm of the College. ❖

Edward Akelman, MD, named Chair of Department of Orthopaedics at Brown

Will also lead programs at RIH, Miriam

PROVIDENCE – **EDWARD AKELMAN, MD**, has been named Chief of the Department of Orthopedics at Rhode Island Hospital and The Miriam Hospital and will become the Chair of the Department of Orthopaedics at the Alpert Medical School of Brown University and the Vincent Zecchino Professor of Orthopeadics, pending the approval of Brown's Corporation.

Dr. Akelman, an internationally known expert in hand surgery and orthopedic education, joined Rhode Island Hospital and Brown University in 1985 and has served as the chief of hand, upper extremity and microvascular surgery for the last 30 years. He replaces **MICHAEL EHRLICH, MD**, who retired late last year.

Dr. Akelman earned his bachelor's degree at Princeton University, and his medical degree at Dartmouth Medical School. He completed his general surgery residency at the Peter Bent Brigham Hospital in Boston, his orthopedic residency at Yale-New Haven Hospital, and spine and hand surgery fellowships at Yale-New Haven Hospital in New Haven and Roosevelt Hospital in New York, respectively.

Dr. Akelman is past-president of the American Society for Surgery of the Hand. He served as chairman of the Council on Education of the American Academy of Orthopaedic Surgeons, and served on its board of directors. He is a past-president of the New England Hand Society and the Rhode Island Orthopaedic Society. He has served on the Board of Trustees at Rhode Island Hospital, on Rhode Island Hospital's Board of Governors and as President of the Rhode Island Hospital Medical Executive Committee. ❖

Vivian Sung, MD, named President of Society of Gynecologic Surgeons

PROVIDENCE – **VIVIAN W. SUNG, MD, FACOG**, a board certified urogynecologist in the Division of Urogynecology and Reconstructive Pelvic Surgery at Women & Infants Hospital of Rhode Island and an associate professor of obstetrics and gynecology at The Warren Alpert Medical School of Brown University, has been named president of the Society of Gynecologic Surgeons (SGS).

Dr. Sung is the principal investigator of the Pelvic Floor Disorders Network (PFDN) grant awarded to only eight sites across the country by the National Institutes of Health, including Women & Infants Hospital. The network is studying innovative, non-surgical and surgical treatments for women suffering from urinary incontinence, pelvic organ prolapse and fecal incontinence.

A resident of Providence, Dr. Sung is a graduate of Tufts University School of Medicine and completed her residency at Magee Women's Hospital at the University of Pittsburgh School of Medicine. She completed a dual fellowship in female pelvic medicine and reconstructive pelvic surgery, and epidemiology and clinical trials at Women & Infants Hospital/Brown University. ❖

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Appointments

Dr. Robert Insoft named to American Academy of Pediatrics Committee

ROBERT M. INSOFT, MD, a neonatologist at Women & Infants Hospital of Rhode Island and associate professor of pediatrics at The Warren Alpert Medical School of Brown University, has been appointed to the American Academy of Pediatrics' Section on Neonatal Perinatal Medicine Steering Committee for the Task Force for Guidelines and Protocol Sharing. Dr. Insoft is also senior vice president and chief medical officer at Women & Infants.

According to Dr. Insoft, "This newly-established committee is charged with the development and publishing of evidence-based clinical guidelines for neonatal medicine nationwide and internationally. It is an honor and a privilege to work with my colleagues from across the nation on ensuring the safest, most effective treatment protocols for some of our tiniest and most vulnerable patients."

Dr. Insoft is an academic pediatrician and neonatologist whose time has been divided among patient care, clinical research, health policy, quality improvement, administration and teaching. Prior to joining Women & Infants, he served as the medical director of the Neonatal Intensive Care Unit (NICU) and Neonatal Respiratory Services at Brigham and Women's Hospital, Boston, where he was also the quality officer in the NICU.

A graduate of Johns Hopkins University and the Boston University School of Medicine, Dr. Insoft completed an internship and residency in pediatrics at Massachusetts General Hospital, fellowships in neonatal-perinatal medicine and intensive care transport in the Department of Pediatrics and the Cardiovascular Research Institute at the University of California, San Francisco. He is also an executive scholar from the Brigham Leadership Program at Brigham and Women's Hospital and Harvard Business School.

Across his career, Dr. Insoft has had the opportunity to contribute to the field of critical care transport and has taught nationally and internationally in this area. He has led the Section of Transport Medicine (SOTM) of the American Academy of Pediatrics (AAP) and is the editor in chief and senior author on the AAP *National Guidelines for Air and Ground Transport of Neonatal and Pediatric Patients, published this past year.* ❖

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Recognition

[L–R] Andy Walter, MD, 2015-16 SGS President; B. Star Hampton, MD, award recipient; and Eric Sokol, MD, 2016 SGS Program Chair.

Dr. B. Star Hampton honored by Society of Gynecologic Surgeons

B. STAR HAMPTON, MD, FACOG, a urogynecologist in the Division of Urogynecology and Reconstructive Pelvic Surgery at Women & Infants Hospital and an associate professor of obstetrics and gynecology at The Warren Alpert Medical School of Brown University, has recently received the inaugural distinguished service award from the Society of Gynecologic Surgeons (SGS).

The Society's distinguished service award is presented annually to one SGS member in good standing who has provided important contributions to the Society. The selection is made by the executive committee and is based on the nominee's scientific leadership, organizational or society service, contributions to the SGS, and gynecological and/or surgical patient care expertise.

Dr. Hampton is a graduate of the Mount Sinai School of Medicine in New York City and completed a residency in obstetrics and gynecology at New York University Medical Center in New York City. Following residency, Dr. Hampton completed a three-year fellowship specializing in urogynecology and reconstructive pelvic surgery at New York University Medical Center. She has achieved board certification in Female Pelvic Medicine and Reconstructive Pelvic Surgery (FPMRS) by the American Board of Obstetrics and Gynecology (ABOG). ❖

Betty Vohr, MD, inducted into Rhode Island Heritage Hall of Fame

Recognized for her contributions in pediatric and neonatal care

PROVIDENCE – Neonatologist **BETTY R. VOHR, MD,** medical director of the Neonatal Follow-Up Program in the Department of Pediatrics at Women & Infants Hospital of Rhode Island and professor of pediatrics at The Warren Alpert Medical School of Brown University, was recently inducted into the Rhode Island Heritage Hall of Fame.

Dr. Vohr has been the director of Women & Infants' Neonatal Follow-Up Program since 1974, medical director of the Rhode Island Hearing Assessment Program (RIHAP) since 1990, and the national coordinator of the National Institute of Child Health and Human Development's Neonatal Research Network follow-up studies since 1990. Dr. Vohr's primary clinical and research interests focus on improving the long-term outcomes of high-risk premature infants and infants with hearing loss.

"I have been fortunate to have had a rewarding career in pediatrics and neonatology at Women & Infants, and I have had the privilege of witnessing the remarkable changes in the care of high-risk infants over the past 40 years," said Dr. Vohr. "There have been amazing strides in the care of low birthweight babies. In 1974, we had one survivor of less than 1,000 grams (2 lbs. 3 oz.); in 2014, we had 108. One of the greatest rewards of doing follow-up for the past 40 years has been witnessing the continued improved outcomes of premature infants."

One of her greatest professional achievements was in bringing forward the issue of universal newborn hearing screening. "Near and dear to my heart is the study that we conducted at Women & Infants that showed the feasibility of newborn hearing screening, resulting in the National Institutes of Health and the American Academy of Pediatrics recommending universal newborn hearing screening in the U.S., with Rhode Island being the first state to comply with these recommendations. Today, more than 98 percent of infants in the U.S. have their hearing screened at birth, and infants with hearing loss now have significantly improved outcomes." ❖

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Recognition

Pamela A. Harrop, MD, (far right), with Elaine Fain, MD and Steven Wartman, MD, was named 2016 Woman Physician of the Year by the Rhode Island Medical Women's Association (RIMWA) at their annual meeting at the Providence Marriott on May 16.

Sidney Migliori, MD, presents **Greg Austin, MD**, with the Rhode Island Orthopedic Society past president's plaque at the May 17 annual membership meeting held at the Chapel Grille restaurant in Cranston. Dr. Migliori is the group's incoming president for 2016–2018.

On May 9 the RI Chapter of the American College of Surgeons/Providence Surgical Society held its annual meeting with a reception and inauguration of its new officers. **Jennifer Gass, MD**, accepted the past president's award. **Adam Klipfel, MD**, was named the new president.

Lifespan Hospitals earn top grades in national patient-safety report

PROVIDENCE – Each of Lifespan's acute care hospitals earned the highest designation possible in the recent "Hospital Safety Scores" report by The Leapfrog Group, a national health care watchdog organization. Lifespan is the only hospital system in Rhode Island awarded an "A" at each of its hospitals as part of Leapfrog's spring report.

Rhode Island Hospital, including Hasbro Children's Hospital, The Miriam Hospital and Newport Hospital were among only five hospitals in the state to receive an "A." Across the country, only 798 of the 2,571 (31 percent) of hospitals graded by Leapfrog received the top mark.

Developed under the guidance of Leapfrog's Blue Ribbon Expert Panel, the "Hospital Safety Score" uses 30 measures of publicly available hospital safety data to assign A, B, C, D and F grades to U.S. hospitals twice per year. These measures include safe practices such as identifying and mitigating risks and hazards as well as infection control procedures such as hand hygiene and proper care of ventilated patients.

The report, calculated by top patient safety experts, is peer-reviewed, fully transparent and free to the public. This year, the report added five new measures of patient-reported experiences with the hospital as well as two common infections, *C. difficile* and methicillin-resistant staphylococcus aureus infections (MRSA). ❖

Recognition

JOHNSON & WALES UNIVERSITY

JWU graduates inaugural class of PAs; nine will practice in RI

PROVIDENCE — On May 19, Johnson & Wales University's (JWU) awarded the Master of Science in Physician Assistant Studies to its first class – a total of 23 students received degrees; nine have accepted job offers in Rhode Island, and two have pending offers.

In 2014, Johnson & Wales' physician assistant program was the first to be offered in the state of Rhode Island. This June, the third class of physician assistants will begin their studies at JWU.

Terrie Fox Wetle, MS, PhD, keynote speaker at the graduation, and Dean of the School of Public Health at Brown, received an honorary Doctor of Humane Letters. ❖

Kent Hospital honors employee service at annual recognition dinner

WARWICK – Kent Hospital honored employees for dedicated service and accomplishments recently at its annual employee awards banquet at Quidnessett Country Club in North Kingstown.

Employees were recognized for their years of service ranging from five to 45 years.

The 2016 Lang Employee of the Year Award was presented to **LISA FERRY, RN**, Outpatient Infusion, who has worked at Kent since 1982.

The 2016 Lang Manager of the Year Award was presented to **JUDITH WOODSTOCK, RN**, Nurse Manager, Patient Care Services, who has worked at Kent since 2011.

Kent's 45-year employees were also recognized for their years of service. They include **LEONARD DUFFY, JR.**, **SHARYN GILLIS, RN**, and **GAIL WILLIAMS, RN**. ❖

Kent Hospital honored Judith Woodstock, RN, and Lisa Ferry, RN, at its annual awards dinner.

Recognition

Gateway Healthcare honors Community Champions at annual awards luncheon

PROVIDENCE – Gateway Healthcare hosted its annual awards luncheon on May 2 and honored individuals and organizations who demonstrate a commitment to their community. Honorees included Bristol Rotary Charities Foundation, Shriners of Rhode Island Charities Trust, Chris Martinez of Procter & Gamble, and **OTIS WARREN, MD**, of the University Emergency Medical Foundation.

Dr. Warren, with the University Emergency Medical Foundation, received Gateway's Champion Award. He was the primary driver for the creation of the Enhanced Care Team, a unique program that promotes emergency room alternatives and care for individuals who live with alcohol and drug dependence. ❖

Southcoast earns 2016 Women's Choice Award

NEW BEDFORD — Southcoast Health has received the 2016 Women's Choice Award as one of America's Best Hospitals for Patient Safety. This evidence-based designation is the only patient safety award that identifies the country's best healthcare institutions based on robust criteria that considers female patient satisfaction and clinical excellence.

"Southcoast Health staff works hard every single day to promote and maintain a culture of safety," said Tim Eixenberger, Chief Nursing Officer for Southcoast Health.

The award winners represent hospitals that have exceptional performance in limiting a wide range of hospital-associated infections and complications from surgery and medical treatment. ❖

Kathleen Carrigan named school nurse teacher of the year for RI

EAST PROVIDENCE – The RI Certified School Nurse Teacher Association recently announced that **KATHLEEN CARRIGAN** has been selected as school nurse teacher of the year for RI 2016.

She has served as District Nurse Coordinator and school nurse/teacher for the City of East Providence for 29 years. She also worked as a pediatric staff nurse at Rhode Island and Hasbro Children's Hospital for 21 years, concurrently with her position in East Providence.

She graduated in 1988 from Rhode Island College (RIC) with a bachelor of science in nursing. She then received her master's of education from RIC in May 2002. ❖

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Recognition

Taro Minami, MD, and Sajid Saraf, MD, honored for teaching by Brown

PAWTUCKET – The Warren Alpert Medical School of Brown University Department of Medicine recently honored eight physicians with the Beckwith Family Award for Outstanding Teaching.

Two of those doctors were Memorial's **TARO MINAMI, MD, FACP, FCCP**, director of simulation and ultrasound training, fellowship site director, Pulmonary and Critical Care Medicine Division of Pulmonary, Critical Careand Sleep Medicine, and assistant professor of medicine (clinical) at The Warren Alpert Medical School of Brown University, and **SAJID SARAF, MD, FACP**, director, Internal Medicine Clerkship Program, associate program director, Internal Medicine Residency Program, and assistant professor of medicine (clinical) at Alpert Medical School.

The Beckwith Family Research and Education Fund was established at Brown through generous gifts from the Beckwith Family Foundation. The endowment fund is used to support the education and research mission of the Department of Medicine, with an emphasis on the education and training of medical residents. ❖

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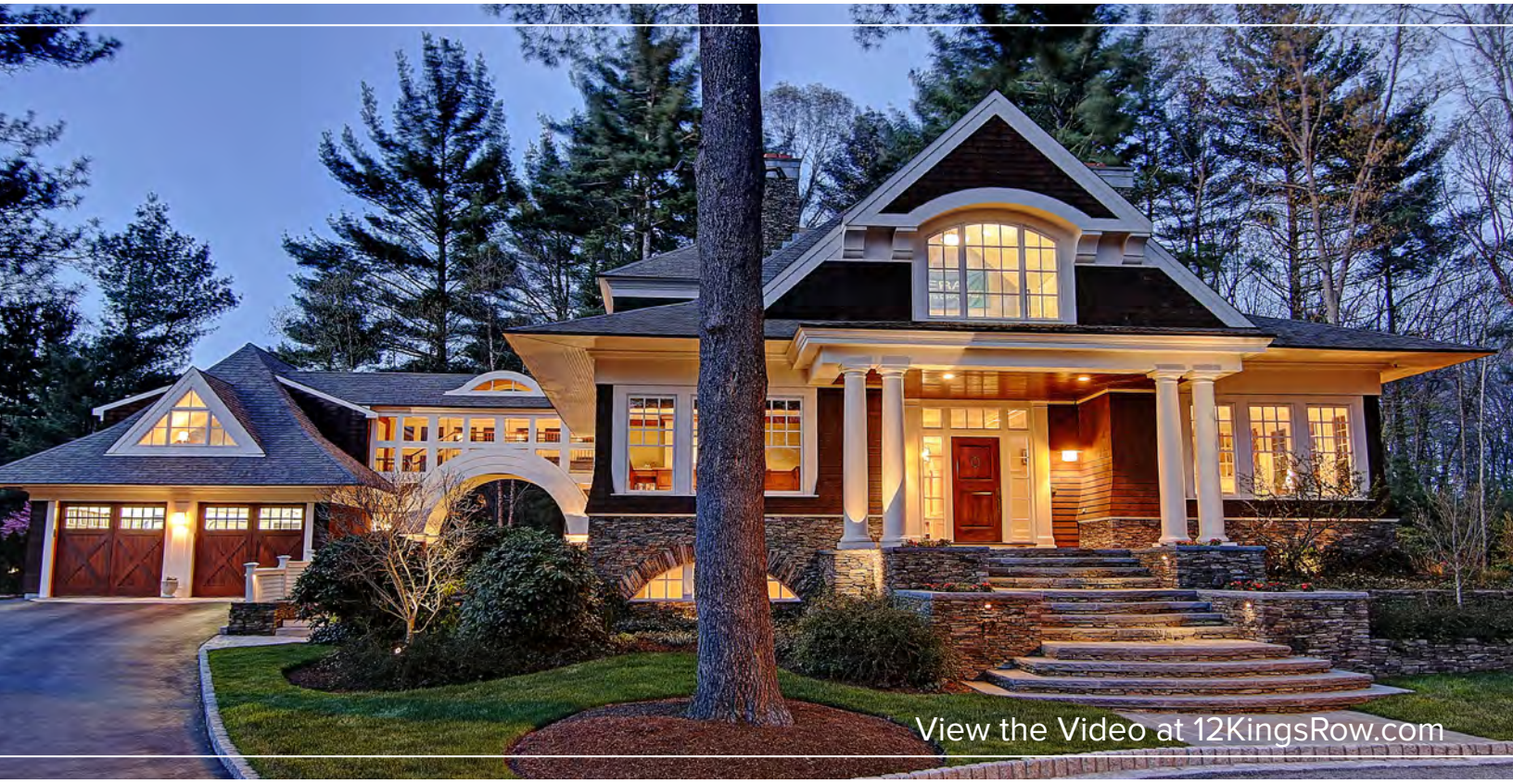

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Obituaries

HARVEY LIBERMAN, MD, 85, of North Kingstown, died peacefully on Wednesday, May 18th at Briarcliffe Manor in Johnston. He was a surgeon at Sturdy Memorial Hospital in Attleboro, Mass., for over 30 years until his retirement in 1996.

During his time there, he served as Chief of Surgery, President of the Greater Attleboro Unit of the American Cancer Society and was a Fellow of The American College of Surgeons. He spent decades as the physician for the Attleboro High School football team and in the late 80's, he also became the Director of Medicine at MetLife Healthcare in Canton, MA.

Harvey grew up in Revere, MA and graduated from Brandeis University and Tufts University School of Medicine. From 1961 to 1963, he was a Captain in the United States Air Force in Turkey. He is survived by his wife Anne (Molloy) Liberman, two daughters Kathleen Hanley and Tamara Liberman of Attleboro, MA, five grandchildren and seven nieces and nephews.

Harvey and his wife were former members of the Wickford Yacht Club where he was Commodore during 2006. He enjoyed sailing, skiing, traveling and was a great fan of all Boston sports teams. He was also an avid reader. A private Celebration of Life will be held to honor the memory of Harvey who touched the lives of so many people. As a surgeon, he was devoted to the care of his patients and was a kind and generous man who was always willing to help someone in need. Harvey will be lovingly remembered by his family and friends.

PAUL L. ROSSIGNOLI, MD, passed away on May 15, 2016. A longtime resident of North Kingstown, Paul was a well-respected otolaryngologist for over 30 years. He was a graduate of Classical High School in Providence, Tufts University and the University of Bologna School of Medicine. He did his residency at Georgetown University in Washington, DC, and was a longtime Chief of ENT at Kent Hospital before retiring in 2000.

In addition to the practice of medicine, Paul was an active member of the Alpine Country Club in Cranston, a member of the AMA and RI Medical Society.

He is survived by his sister Paula (Rossignoli) Recchia and her husband Richard O. Recchia, MD, of Cranston; and several nieces and nephews.

In lieu of flowers, memorial contributions may be made to Gentiva Hospice, 2374 Post Rd., Suite 206, Warwick, RI 02886.

ALEXANDER S. RUHIG, MD, 87, passed away peacefully on May 22, 2016. Born in Hungary, he survived the Nazi persecution of World War II and attended the University of Graz where he received his medical degree in 1955. He emigrated to the United Stated where he obtained his license to practice medicine in Rhode Island in 1961. He specialized in psychiatry providing care to patients in Rhode Island and Massachusetts over a long career.

He enjoyed skiing the glamour resorts of Europe for many years along with tennis in the summer and sailing with friends on Narragansett Bay. Alex is survived by his loving nieces and dear friends throughout the world. He will be missed by all for his unique personality and love of life (and food).

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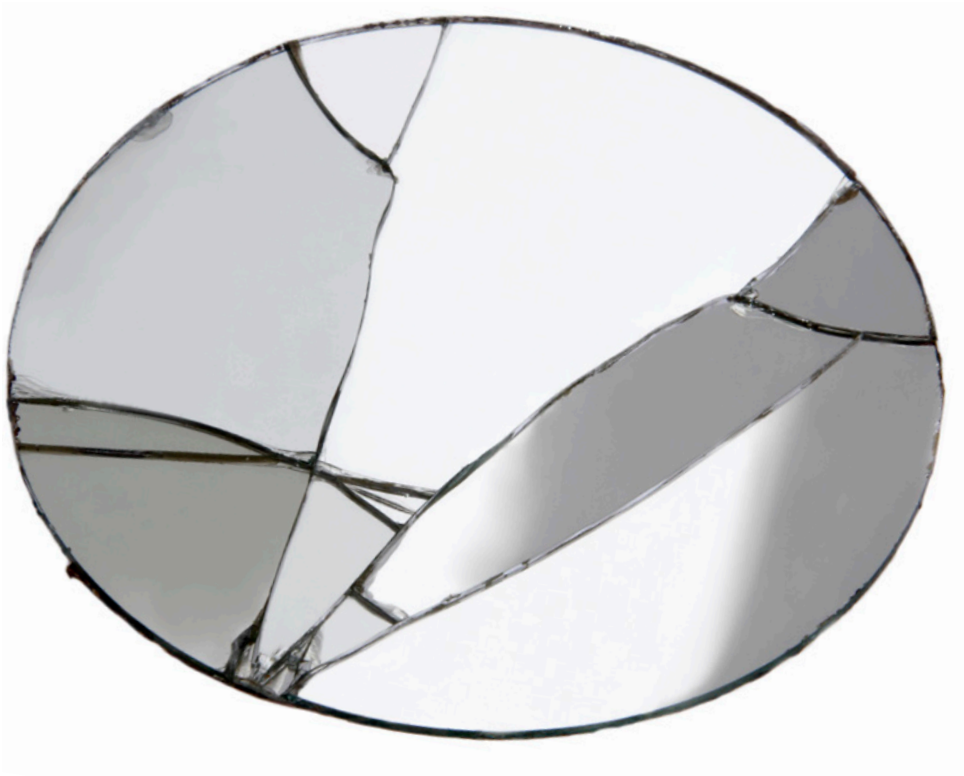

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A Last Hurrah: Memorial's Nurse Alumni Association Celebrates Centennial

SUSAN McDONALD

Pawtucket nurse introduces a newborn to the infant's soldier father.

PAWTUCKET – For 59 years, from 1911 to 1970, the Memorial Hospital Training School for Nurses, later called the Memorial Hospital School of Nursing, trained women ages 18 to 25 as nurses. In 1916, the same year the first formal presentation of diplomas to school graduates was held, nine graduates formed the Nurse Alumni Association.

Members of the organization – many of whom stayed working at Memorial Hospital through the years – celebrated their group's 100th anniversary with a spring banquet May 18, at Kirkbrae Country Club in Lincoln. The event included the final business meeting of the association, which will dissolve due to lack of leadership.

Janet Sherman of Lincoln, the president of the Nurse Alumni Association since 2010 who retired in 1995 as a nurse in Memorial's post-anesthesia care unit (PACU), talks about being in nursing school in the 1950s.

"At first, I wanted to be an airline stewardess," she laughs. "But, there was a prerequisite that you had to be a nurse to be a stewardess. And my older sister was a nurse. I really just wanted to be of service to people."

Service-minded

It was a similar calling that brought almost 1,000 men and women to the Pawtucket campus of Memorial Hospital, to a nursing school housed in an old Victorian manor donated to the hospital by the Goff family in 1910. The third floor of the home was the dormitory where students, under the watchful eye of house mothers who enforced curfews and lights out at 10 o'clock.

Clad in blue-checked chambray uniforms with long skirts and high collars, the first students were instructed to move into the dormitory with "one napkin ring, two pairs of black shoes or boots, and four sets of plain underclothing."

With as little as one year of high school completed, the students worked in the hospital – which in the early 20th century consisted of one building with wards for men, women and children, and outpatient services – either from 7 a.m. to 7 p.m., or 7 p.m. to 7 a.m. They had one hour off a day, one afternoon a week, and three hours on Sunday for "rest, study and relaxation." When off duty, they went to class taught by the medical staff in subjects like bacteriology and surgical nursing, and were expected to be ready for emergencies.

Their first clinical rotation, however, was always in the operating room, where Sherman says they "could understand why people were in pain."

Through various affiliations forged through the years, the nursing students at Memorial worked in the community with the visiting nurses, in the armed services during the war years, and at other hospitals in the area, including Butler Hospital, currently part of Care New England with Memorial.

Sherman remembers her rotation at the former Charles V. Chapin Hospital, where patients with infectious diseases like tuberculosis and polio were treated.

"We were always gowned, gloved and masked to protect us," she explains, noting that her time at Chapin was at the height of the polio epidemic during the 1950s.

The nurses of the mid 20th century.

PHOTOS COURTESY OF MEMORIAL HOSPITAL/CARE NEW ENGLAND

The original Victorian-style Goff Building, site of the first nursing school and donated to the hospital by Pawtucket's Goff family in 1910.

A different era

In addition to the specific uniforms and caps, the design of which designated which nursing school a woman had graduated from, the training and practice of nursing was very different than it is today, Sherman continues.

She trained in the cardiac care unit and remembers the advent of the 911 emergency system. It was a time when doctors may have depended on the nurses to help with the patients, but the nurses were required to stand when the doctors walked into the room to show their respect.

It was also a time when getting pregnant meant you resigned from your job. Many women would return once their child had grown to school-aged but they had to reapply and be rehired. Only single students were enrolled at Memorial's School of Nursing and yearbooks in the 1960s would include designations such as "first bride" or "second bride" with personal quotes beside the graduate's photo.

"It was good psychologically for us, too. We were more naïve back then," Sherman begins. "But, living in the nurses' home, we needed to learn to work with different people. It was good training."

Helping future nurses

The Nurse Alumni Association has given back to hospital for a century, organizing and participating in fundraising events. In addition, the group established the Esther A. Watson Scholarship Endowment Fund at the University of Rhode Island (URI), which Sherman says will serve as the members' legacy.

Named for a long-time nursing director at Memorial and a graduate of the Memorial School of Nursing, the scholarship was created in 1970 and is awarded each year to a nursing major through the URI Foundation.

The scholarships will continue after the group dissolves, and any money left in the treasury will be put into the fund. Going forward, all Nurse Alumni members in good standing will be awarded lifetime memberships and their ancestors will be given added consideration for the scholarship.

Sherman says she regrets having to take the drastic step of dissolving the group but no one has stepped forward to take over the helm.

"It's with great sadness and regret that we've come to the decision to dissolve the Alumni Association," she says. "We all have fond memories of our nursing school days but there is no one interested in leading the group and it's time I step down." ❖

Susan McDonald is Marketing Communications Manager of Memorial Hospital and Senior Editor, Women & Infants Hospital.