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20 YEARS *** ANNIVERSARY ***

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Medical Journal of Southern California CLINICIANS

A peer-reviewed journal of healthcare and medical science.

IN THIS ISSUE

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Mission and Purpose

The Medical Journal of Southern California Clinicians was established by the Medical Staff of Pomona Valley Hospital Medical Center in Pomona, California. It provides a journal for modern California clinicians to publish articles to share their clinical experiences and opinions with other physicians, show their academic achievements in medical practice, and keep a permanent record of valuable case studies and case reports from all departments and all specialities in the modern era.

This journal invites all clinicians in southern California to contribute evidence-based articles and reviews, including new developments in clinical skills and techniques, or new procedures applied during their medical practice.

In order to maintain the highest quality, accuracy and academic dignity, all articles are peer reviewed. Articles will be reviewed by our editorial board and special consultants.

As a self-supported publication, we welcome and depend upon your generous contributions for support. Please contact Dr. Yin Lai by email at *yinhlai@gmail.com* to make a contribution.

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Preface for 20th Anniversary

Yin H. Lai, MD

Editor-In-Chief

Yin H. Lai, MD

Congratulations! This is the **20th anniversary** for *The Medical Journal of Southern California Clinicians* (MJSCC).

In 2000, we decided to publish a medical journal to provide a venue for local clinicians to share their clinical experiences, for medical students to have opportunities to write papers with their mentors, and for the local hospitals, medical groups, and pharmacy/drug stores to share their services.

In that same year, the first editorial board was organized and the Pomona Valley Hospital Medical Center medical staff approved the journal. However, the pregnancy took three years before the first baby journal was delivered in 2003. Over the past years, with the help of local medical communities, the journal's circulation has gradually increased in the communities of Pomona, Upland, Ontario and Chino. To reach more readers, the editorial board decided to expand the journal to Open Access so content can be accessed free of charge, online, at www.SoCalClinicians.org as well as by traditional hard copies, which will be delivered to our readers' doorsteps through the mail.

I want to thank our journal staff and editorial board members involved in making this journal not only possible but to flourish. I also want to extend my gratitude to all author-contributors, readers, subscribers, and supporters. Without their involvement, we couldn't have made it this far.

Due to the COVID-19 crisis, the celebration for the 20th anniversary of MJSCC is cancelled. This epidemic coronavirus infection is the worst humanitarian disaster since World War I. While COVID-19 is now killing 6,000 people worldwide a day, we are grateful to many doctors and nurses working hard in the hospitals. They risk their own lives working in the hospitals every day and night, offering their precious boundless love, touching patients with insufficient and sometimes uncertain quality PPE.

By the publication of this issue, countless doctors and nurses have died during their holy duty of treating patients suffering from COVID-19. These heroes and heroines deserve the highest respect and honors and we extend our deepest sympathy to their broken families who are suffering and in need of tremendous emotional and financial support.

May God Bless America and all humankind!

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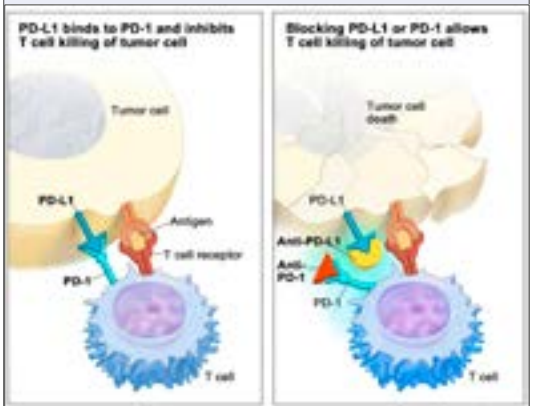
An Oncologist's view on What Kills COVID-19 Infected Patients?

Dr. Lai,

For a long time, we, as oncologists, have tried every possible means to boost up a patient's immune system so that the cancer cells can be killed. As if adding more gas and fuel into the immune cells will increase their ability to recognize and kill the cancer cell in the body which eventually lead to the usage of BCG, Interferon-alpha and Interleukin-2 (IL-2) treatment.

When Dr. Steve Rosenberg at the NIH published the result of high dose IL-2 treatment in patients with metastatic melanoma in 1986 (subsequently renal cell carcinoma), we were all very excited. The most serious side effect experienced by patients was vascular leak syndrome (VLS) also called capillary leak syndrome, which is caused by binding of IL-2 to high-affinity IL-2 receptor on the surface of vascular endothelial cells and increased vascular permeability. Thus, causing extravasation of the intravascular fluid into the surrounding third space causing shock, MI, etc. Also, it can lead to life-threatening pulmonary complications and if this happens in the brain, this could cause brain edema. Therefore, all of the patients that received this treatment required ICU admission.

FIGURE 1.
Immune checkpoint inhibitor



Courtesy from NIH

In addition, the follow-up result was somewhat disappointing with only 6% long term survivors. This is the reason why this type of immunotherapy is rarely used nowadays.

It wasn't until early 2000 when researchers began to realize there is a brake system (CTLV-4, PD-1) on the surface of immune cells that helps them maintain their function properly in order not to damage the bystander host cells while they are fighting the invading organisms during infection. In addition, this brake system is designed to prevent the immune system from causing autoimmune disorders. PD-1 on the surface of immune cells in cancer patients prevent them from recognizing and killing cancer cells as foreign to them as well.

Whereas the surface protein PDL-1 on the malignant cells helps them to escape from detection and killing by the immune cells of the cancer patients. The development of immune checkpoint inhibitors to block PD-1 or PDL-1 and prevent the binding of PDL-1 to PD-1, allows the immune cells to kill cancer cells. (FIGURE 1)

The discovery of immune checkpoint drugs to treat metastatic melanoma and other types of cancer eventually lead to The Nobel Prize for Physiology and Medicine being awarded to Dr. James Ellison from the U.S. and Dr. Tasuku Honjo of Kyoto University in Japan in 2018.

This type of immunotherapy is currently used to treat multiple cancers, including melanoma, non-small-cell lung carcinoma, glioblastoma, mesothelioma, and renal cell carcinoma, etc. Despite impressive survival benefits through the use of immunotherapy in patients with melanoma and NSCLC, its use can be hampered by the occurrence of serious adverse events related to excessive immune activation, collectively named as immune-related adverse events (irAEs).

This over-activation can potentially affect multiple organ systems including the lung, the gastrointestinal tract, kidneys, nervous system, liver, eyes, skin, pancreas and endocrine system. Many of the conditions can be life-threatening calling for the discontinuation of immunotherapy and using a long-term corticosteroid; at times, anti-tumor necrosis factor therapy.

Given the observation of adverse effects of both IL-2 therapy and immune checkpoint inhibitor (immunotherapy),

I think those young adults who got into serious trouble from Covid-19 infection might have been caused by a similar mechanism with an overwhelming immune response which not only kills the Covid-19 virus but also their own host lungs as an innocent bystander.

Sincerely,

Shu-Dean Hsu, MD

Board Certified in Internal Medicine,
Medical Oncology, Hematology/Oncology
Sequoia Regional Cancer Center, Visalia, CA

Free 2019-nCoV Health Learning Module

Dr. Lai,

WiRED International's medical writing team has prepared a FREE health learning module on the Coronavirus infection. The information and guidance are from the world's most authoritative sources: The World Health Organization and the Centers for Disease Control and Prevention. This module is useful as general introduction to the new coronavirus (2019-nCoV) and describes the infection and its close relationship to other coronaviruses, how it is spread, its incubation period and symptoms, treatment and most important — its prevention. Please share the link to the module with your readers:

http://www.wiredhealthresources.net/presentations/990/story_html5.html

Suellen Crano, PhD
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Thyroid Hormone Resistant Syndrome

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KEYWORDS:

Elevated Thyroid Hormone Levels , Endocrinology, THR, Thyroid Hormone Resistance

ABSTRACT

Thyroid hormone resistance (THR), also known as resistance to thyroid hormone (RTH), is an inherited condition characterized by reduced end-organ responsiveness to thyroid hormone, caused by mutations in the thyroid hormone receptor gene. Patients typically present with elevated thyroid hormone levels (T3 and T4) with normal, or slightly elevated thyroid stimulating hormone (TSH) levels.[1] In a majority of cases, the disease is caused by a mutation in the thyroid receptor beta (TR-beta) gene. Patients can present with signs and symptoms of hypothyroidism or hyperthyroidism or can be asymptomatic. We present a case of a 16-year-old male who was referred for endocrinologic evaluation after abnormal findings in the thyroid function panel.

INTRODUCTION

Resistance to thyroid hormone (RTH) is an autosomal dominant disorder characterized by reduced end-organ sensitivity to thyroid hormone, leading to elevated levels of T4 and T3 accompanied by normal or slightly elevated levels of TSH. The syndrome has a prevalence of about 1 in 40,000 live births, occurring with equal frequencies in both sexes.[2] The overwhelming majority of cases are caused by mutations in the thyroid receptor -beta gene, interfering with the physiologic function of the thyroid receptor.[3] Thyroid hormone has a variety of functions on many different tissue types and organs in the body. The severity of hormonal resistance varies among different tissue types, probably due to the variable expression of thyroid receptor throughout different organs.[4]

Due to the decreased sensitivity to thyroid hormone, the elevated levels of T4 and T3 fail to downregulate the production of TSH from the anterior pituitary gland, as demonstrated by the normal or elevated TSH lab values. Patients can be asymptomatic, or can present with either hypothyroid (growth retardation, delayed bone maturation, learning disabilities, sensorineural deafness) or hyperthyroid (tachycardia, hyperactivity, increased basal metabolic rate) features.[5] With labs that mimic hyperthyroidism and a nonspecific clinical presentation, patients can be misdiagnosed and even unnecessarily treated with invasive techniques (radioactive iodine ablation) that can further exacerbate the underlying 'hypothyroidism'. Treatment is not indicated in a majority of cases as the hyposensitivity to thyroid hormone is

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adequately compensated by the increased thyroid hormone levels.[6] Patients who develop a large goiter due to increased TSH levels can be treated with high-dose triiodothyronine to help regress the goiter.[7]

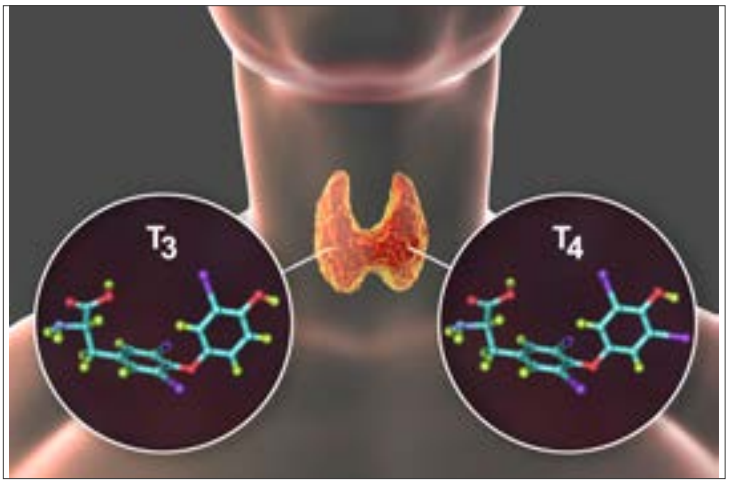
In the following case, we will discuss a patient who presented with poor weight gain, learning disabilities and bilateral sensorineural hearing loss. The patients' laboratory workup revealed elevated thyroid hormone levels accompanied by normal TSH levels without any overt signs of hyperthyroidism or hypothyroidism.

CASE:

A 16-year-old male patient was diagnosed with Resistance to Thyroid Hormone at the age of four-and-a half years old when thyroid function tests revealed elevated total T4, free T4, T3 and normal TSH levels, without any obvious clinical signs of hyper- or hypothyroidism. The patient initially presented with poor weight gain and low BMI (his most recent labs reveal his height and weight to be <1 percentile and his BMI at 4th percentile). At that time, the patient's bone age was determined to be six years-old (when his chronological age was 4.5 years-old). This was thought to be secondary to the relatively increased sensitivity to thyroid hormone in certain tissues, such as bone. Both his parents, and siblings had thyroid function tests completed, and tested normal.

Past Medical History

The patient was born at 37 weeks gestation, with no complications, no history of gestational diabetes, intrauterine growth restrictions (IUGR) or small for gestational age (SGA). The patient was diagnosed with bilateral sensorineural hearing loss, for which he uses hearing aids. He has learning disabilities and is currently in special education. Earlier on, during childhood development, there was a concern for possible attention deficit disorder (ADD) for this patient,[8] but this is no longer a concern as he does not demonstrate signs of the disorder. He has no other prior hospitalizations or surgeries. The patient has seasonal allergies, and he is allergic to Amoxicillin (develops a rash upon exposure).



Family history

Family history is negative for thyroid hormone resistance or any other thyroid pathology, as confirmed by normal thyroid function tests completed by both parents and his siblings. The mother's height is 4'8" and father's height is 5'2", therefore, the patient's short stature is within his mid-parental target height. The patient was, however, growing above his genetic potential but due to his advanced bone age, has obtained an adult height of 5'1.58" at the age of 16.

Physical Exam

On physical exam, he has a blood pressure of 117/57, a pulse of 67, temperature of 37° C, weight of 92 lb 13oz (<1 percentile), and a height of 156.4cm (<1 percentile). His BMI is at the 4th percentile (Figure 1). The patient appears in no acute distress, with no dysmorphic features, but is thin. He demonstrates delayed, slow responses but is interacting well and answering appropriately for the most part. Examination of the eyes shows mild bilateral proptosis. No thyromegaly or thyroid nodules are noted on examination of the neck. Neurologic exam is non-focal. Patellar and brachioradialis DTRs are 2+ bilaterally. The patient also has bilateral sensorineural hearing loss and uses hearing aids.

LABORATORY STUDIES

Laboratory results consistently demonstrate normal TSH but elevated Total T4, Free T4 and Total T3. These findings are indicative of end-organ resistance at the anterior pituitary gland (Table 1). Based on the negative feedback principles of functional physiology, we expect elevated values of T4 and T3 to suppress TSH production. The normal values of TSH indicates lack of negative feedback, due to thyroid hormone receptor polymorphism which inhibits physiologic hormone signal transduction.

TABLE 1.
Laboratory Findings on Thyroid Panel

	LATEST REFERENCE RANGE	1/31/2018
T4. TOTAL	4.5 – 12.0 mcg/dL	27.5 (H)
TSH	0.50 – 4.30 ML U/L	1.29
	LATEST REFERENCE RANGE	9/15/2016
T4, FREE	0.8-1.4 ng/dL	4.6 (H)
T3, TOTAL	86-192 NG/DL	313 (H)
TPO AB (Q)	<9 IU/ML	1
TSH	0.50 – 4.30 MI U/L	1.66
	LATEST REFERENCE RANGE	3/14/2016
T4, TOTAL	4.3 – 12.5 ug/dL	23.9 (H)
TSH	0.35 – 5.00 UL U/L	1.76

SNP microarray

46XY with normal copy number. High density of short contiguous regions of homozygosity. Per genetics: *this suggests an increase in autosomal recessive allele risk.*

Impression and plan

The patient is a 16-year-old male who presents with growth delay, intellectual disabilities, bilateral sensorineural hearing loss and lab values demonstrating consistently elevated thyroid hormone with normal TSH levels. He is clinically euthyroid. Although no further genetic analyses were done, his clinical presentation and lab findings are consistent with thyroid hormone resistance, most likely secondary to a mutation in the thyroid receptor-beta gene. He does not have a family history of THR, which indicates either a de novo mutation or possibly, autosomal recessive transmission.

The primary differential diagnosis in this case would be a TSH-secreting pituitary adenoma, given his elevated thyroid hormone levels and unsuppressed TSH. However, the patient doesn't show signs of a pituitary adenoma as he does not have any mass-effect findings (bitemporal hemianopsia), thyromegaly or other hormonal derangements (pituitary adenomas co-secrete). Furthermore, the patient does not demonstrate the classic signs of hyperthyroidism that would be present in a TSH-secreting pituitary adenoma (palpitations, tachycardia, unintentional weight loss, heat intolerance, insomnia, restlessness).

Since the patient is clinically stable and his developmental delay is not profound, he is currently not undergoing any treatment with thyroid hormone. Certain cases of THR require supraphysiologic doses of levothyroxine to overcome end-organ resistance. The patient is currently under the care of endocrinology, following up with yearly laboratory studies. He is also under the care of pediatrics, for continued management of weight trends.

DISCUSSION

We describe a case of a 16-year-old male with poor weight gain, bilateral sensorineural hearing loss and intellectual disabilities. Further laboratory studies revealed elevated thyroid hormone levels in the setting of normal TSH values indicating a failure to suppress TSH production. The clinical presentation and laboratory findings are indicative of THR. The syndrome is characterized by decreased peripheral and pituitary sensitivity to thyroid hormone due to mutations in the thyroid receptor-beta (TR-beta) gene located on chromosome 3.

THR is detected in about 1/40,000 live births with an overwhelming majority demonstrating autosomal dominant inheritance pattern. It is particularly interesting to note, that in our case, there is no pertinent family history of thyroid hormone resistance or any other thyroid hormone pathology. Lack of positive family history combined with his SNP microarray assay which demonstrates a high density of short contiguous regions of homozygosity, the patient in this case likely developed the syndrome due to an autosomal recessive inheritance[9] or a de novo mutation in the TR-beta gene.

Common clinical findings encountered with THR include goiter (65-95% of cases), hyperactivity (33-68%) and tachycardia (33-75%).[10] These clinical signs combined with the laboratory findings of elevated thyroid hormone levels often results in the erroneous diagnosis of hyperthyroidism. Patients are subsequently subjected to ablative or antithyroid treatment to reduce thyroid hormone levels, which can further exacerbate an underlying 'hypothyroid' state. It is therefore critical for physicians to recognize the presentation of THR in order to carry out proper management of the syndrome.

The patient in our case did not demonstrate any of the classic findings of hyperthyroidism (goiter, hyperactivity, tachycardia). Instead, he presented with findings such as poor weight gain, low BMI, bilateral sensorineural hearing loss, and learning disabilities. These findings have been reported in patients with thyroid hormone resistance, but at reduced rates. The poor weight gain and low BMI can be explained by the elevated thyroid hormone levels, since the degree of insensitivity to thyroid hormone varies throughout different body tissues. Studies have demonstrated that patients with THR have increased muscle-derived resting energy expenditure as a consequence of thyroid hormone-mediated mitochondrial uncoupling.[11]

The patient's bilateral sensorineural hearing loss can also be explained by his THR. Studies have demonstrated the importance of TR-beta in the development of the inner ear. Studies on mice have shown that the absence of TR-beta-1 gene is sufficient to cause hearing loss.[12]

There is a high prevalence of learning disabilities in patients with thyroid hormone resistance. In a study carried out to describe the genetic and clinical features of thyroid hormone resistance, 38% of the subjects were found to have an IQ < 85 and 35% had speech impediment. Thyroid hormones play a critical role in brain development with their influence on neurogenesis, neuronal migration, neuronal and glial cell differentiation, and synaptogenesis. The actions of thyroid hormones are carried out through hormonal interaction with intranuclear receptors, leading to regulation of gene expression. Studies conducted on mice expressing a mutant TR-beta-1 gene demonstrated properties similar to those seen with severe hypothyroidism, such as neuromotor disability.[13]

Treatment is not required in a majority of cases of THR as the elevated thyroid hormone levels tend to compensate for the decreased end-organ sensitivity. However, certain groups of patients do require treatment to manage their symptoms. Patients who have been erroneously treated for hyperthyroidism with ablative therapy require thyroid hormone supplementation to decrease TSH levels to normal. These patients have a decreased thyroid hormone reserve, requiring supplementation. Certain patients, however, develop goiters and thyromegaly. Regression of large goiters has been successfully achieved with the administration of a single high dose of Liothyronine (L-T3) given every other day.[7]

In certain patients with THR, peripheral tissues may be relatively more resistant than thyrotropes in the anterior pituitary. This can lead to inadequate compensation for the hormonal resistance in these tissues. In these cases, T4 administration beyond stabilization of TSH levels is required. The adequate dose needs to be determined on an individual basis by regularly assessing the patient's response to thyroid hormone. This should be carried out with regular assessment of growth, bone maturation, and mental development over long-term care. Since our patient is clinically euthyroid, has obtained mature adult height and his developmental delay is stable (he is in 11th grade, special education), the endocrinologist has decided against treatment with thyroid hormone. The patient is under the care and management of endocrinology and pediatrics with regular laboratory studies and assessment of weight changes. He has been showing improved signs of increasing BMI percentiles.

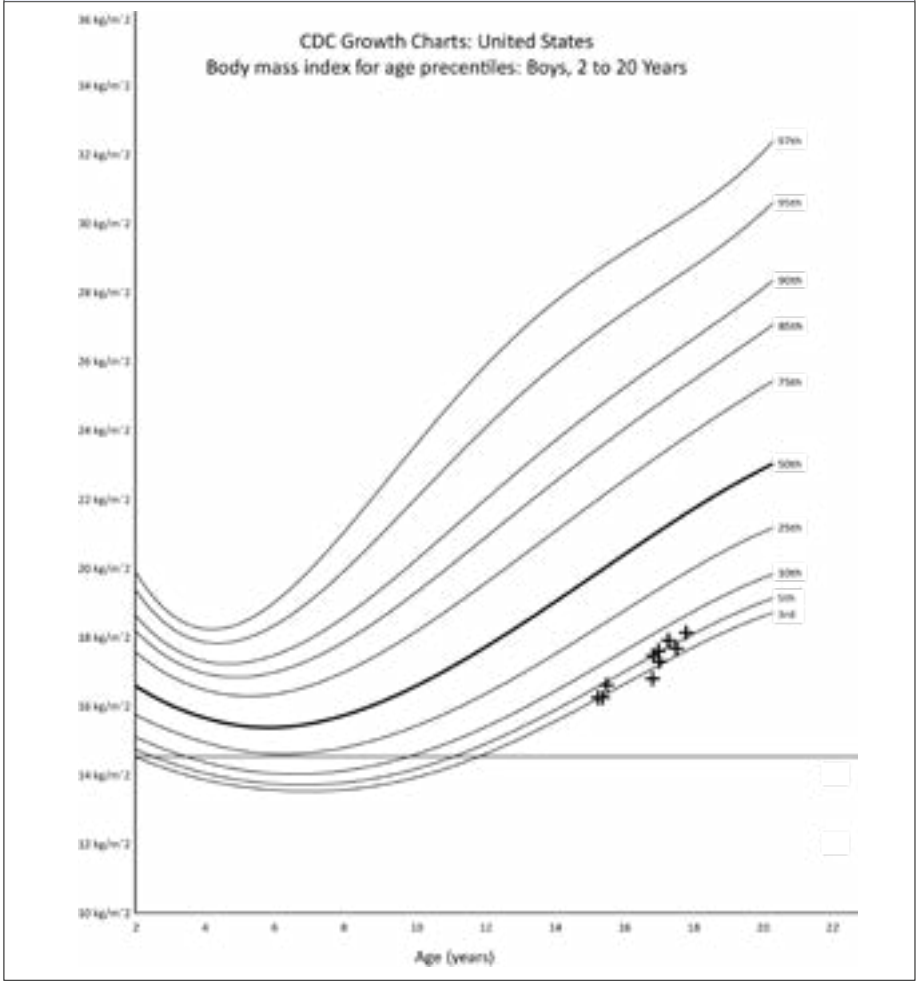
As depicted in the growth chart (Figure 1), the patient consistently falls at or below the 5th percentile in the BMI Growth charts. The low BMI can be explained by the increased levels of circulating thyroid hormones. The patient's most recent weight was 92lbs and 13oz. Studies have demonstrated that patients with THR have increased muscle-derived resting energy expenditure as a consequence of thyroid hormone-mediated mitochondrial uncoupling. The patient's most recent height was measured at 156.4cm. The short stature of the patient can be explained by the average height of his parents (mother, 4'8" and father, 5'2") and also, due to his increased rate of bone maturation, secondary to thyroid hormone.

AUTHOR DISCLOSURES:

No relevant financial affiliations or conflicts of interest.

FIGURE 1.

Patient's Trends on BMI Growth Chart



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Urgent Care Fellowship Targeting Family Medicine Graduates

Kenneth Moore, MD

Pomona Valley Hospital Medical Center, Pomona, CA

The Emergency Department at Pomona Valley Hospital (PVH) has developed a one-year Urgent Care Fellowship. It is intended for Family Medicine graduates to provide them with advanced training in Urgent Care procedures and techniques. PVH began the program in 2015 in conjunction with the Family Medicine Residency Program and under the auspices of the Hospital and the GME Committee. We have had five Fellows since the program's inception. Two have been interested in Emergency Medicine and we geared the program toward those skills and needs. The others have had lots of experience in routine Urgent Care procedures such as laceration repairs, foreign body removals, nosebleed treatments, abscess incision and drainage, use of lab and x-ray, ultrasound techniques and so forth. In addition, they have had experience with advanced procedures such as fracture care, reduction of dislocations, complex laceration repair and the like. A big part of the training is learning when to treat and when to refer.

Our Fellows spend most of their time in the ER but also have some experiences outside of the department. They spend two weeks learning from our Radiologists, one week in an Ophthalmology office, one week at the Western University School of Dentistry and one week in a Dermatology office. They also spend some time in the Hospital's Urgent Care Centers. They go to two CME conferences throughout the year and there are several training sessions in wound care, suturing, splint placement and slit lamp use.

Our graduates have moved on to:

- Work in the Pomona Valley Hospital affiliated Urgent Care Centers
- Work in an Urgent Care Center in Oregon
- Work in an Emergency Department in Canada
- Work in an 'Advanced Urgent Care Center' in Glendora
- Our current Fellow will be working in an Emergency Department in Northern California after graduation in July

Beginning in August 2020 we will be having two Fellows, both are interested in working in Urgent Care facilities in the future. At this time Urgent Care Medicine is not ACGME approved as a specialty. But the field is growing and interest is increasing. There are several organizations that are not ACGME but do confer certification in Urgent Care Medicine. Two of the organizations confer Board Certification after appropriate examinations.

We have been very happy with the program and with our graduates. They have brought a new dimension to our Emergency Department practice and it gives us an opportunity to train future Urgent Care physicians. We hope to continue having two Fellows each year in the future.

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The Role of 3D Imaging in the Practice of Medicine and Medical Education

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ABSTRACT

Technology has revolutionized the practice of medicine. X-rays were the gold standard of imaging for many decades, but in recent years 3D imaging technology has been developed to represent the exact anatomic, pathologic disease processes. In medical practice, 3D images can be obtained by a variety of methodologies, including 3D laser scanning, computerized tomography (CT), and magnetic resonance imaging (MRI). Since 3D imaging technologies have been incorporated into the health field, it has made tremendous advancements in all aspects of medicine, including orthopedic surgery, neurovascular surgery, forensic pathology, pathology, and dentistry. 3D imaging can be used not only for diagnostic services, but also as treatment modalities. In addition, 3D imaging has also made an impact in medical and allied health education. From the 3D scanners used to produce optimal reconstruction of surgical pathology specimens to the fluoroscopic 3D imaging used to aid orthopedic surgeons in surgery strategies, the purpose of this review is to explore the current literature to illustrate the impact of 3D imaging on medical practice and to also discuss future applications.

INTRODUCTION

Technology has revolutionized the practice of medicine. We are dependent on technology in virtually every field of medicine. In 1895 when X-rays were introduced, it was the gold standard of imaging for many decades.[1] Given that an X-ray radiograph is a 2D image, there are certain limitations of capturing a 3D object in the two-dimensional field. Structures superimpose on each other, and it becomes difficult to appreciate the pathologic processes in situ.[2] 3D imaging technology was developed to circumvent this issue and represent the model of the anatomy and pathological disease processes more accurately.

Current imaging methods include ultrasound, computed tomography (CT), and positron emission tomography -CT (PET-CT), all producing 2D images, but with the evolution of technology, the use of 3D imaging has quickly established a prominent role in the practice of medicine.[3] Given the potential of this growing field, literature on 3D imaging has increased exponentially over the years, illustrating the broad range of applications for the new technologies. From the 3D scanners used to produce optimal reconstruction of surgical pathology specimens to the fluoroscopic 3D imaging used to aid orthopedic surgeons in surgery strategies, the purpose of this review is to explore the

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current literature on how 3D imaging is currently impacting medical practice and secondarily and to discuss future applications of 3D imaging.

HISTORICAL BACKGROUND

3D imaging has become a critical emerging technology in the healthcare field. Many complex medical procedures, diagnoses, and treatments are possible today with the advancement of 3D imaging. In 1895, the first X-ray image of the human bones was reproduced by Wilhelm Roentgen and this revolutionized medicine.[3] In 1972, X-rays CTs were introduced by Godfrey Hounsfeild in the medical field to noninvasively view the human body.[4] CT scans generate images by using X-rays beams to scan the human anatomy while the recorded images are transmitted to a computerized system for radiologists to view.[5] They have transformed our knowledge resulting in a deeper understanding of pathological processes, an important step in the diagnosis of diseases. Since its development, CT has greatly impacted the health field and today it has become the fundamental building block of 3D imaging.

In 1986, Charles Hull developed 3D laser scanning, another addition to 3D imaging, which has also impacted the healthcare field.[6] 3D scanners use lasers to digitally recreate identical computerized images of the anatomical structure of interest. With the images from the 3D laser scan, clinicians are able to make an exact 3D anatomical replica through a 3D printer. Many of these anatomical replicas are useful to clinicians as it allows them to study the patient's anatomy in diseased states.

In 2006, 3D imaging led to the development of Multiple Detector Computer Tomography (MDCT), a 3D technology that uses X-rays from CT scans to capture multiple cross-sectional images and reconstructs them to form 3D images.[7] MDCT has contributed to the advancement of our clinical knowledge in comparison to a single-detector CT.[7] For example, MDCT has allowed clinicians to view image slices of a patient's anatomy within minutes. It is capable of generating high resolution images with improved temporal and spatial depth.[7] These images are stored in a Picture Archive and Communication System (PACS). PACS was developed in the 1990's[8] as an image storing database which provides clinicians with a convenient interface to save, organize, and manipulate recorded images from many imaging technologies such as MDCT. The technologies described above have allowed for a rapid, non-invasive, and cost-effective 3D reconstruction of the anatomic structure.[7]

FIGURE 1.
A line of laser light projecting onto the surface, while sensors record displacement of laser light.

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METHODOLOGY

In medical practice, 3D images can be obtained by a variety of methodologies, including 3D laser scanning, CT, and magnetic resonance imaging (MRI).[3] In 3D laser scanning, the object of interest is placed on a digitizer bed. A line of laser light is projected onto the surface while two sensors record the displacement of the laser light, demonstrating the changing contour and shape of the object (Figure 1). Scanning can be performed using stationary scanners, handheld scanners, an image of which is shown below, and smartphones that have been integrated with 3D scanning technology.[9]

The CT scanner generates an X-ray that creates a snapshot image that is recorded by a detector on the opposing side. These cross-sectional images are taken in succession until the desired area is fully imaged, then they are combined for a 3D image[3]. In MRI, radio waves are sent by the machine with the purpose of stimulating hydrogen atoms within cells. The hydrogen atoms emit energy that is converted to numbers. The numbers are processed in a computer and an image is produced.[3]

3D imaging consists of 3D scanning, modeling, and printing. It is the process of producing a digital representation of an object. 3D scanning can be used to generate 3D models and 3D prints of an object and uses computer software to take a collection of data points from the scanned image and recreate them in a three-dimensional space. 3D printing is the process of producing a tangible object from a computer aided design model, which is often interchangeably called

additive manufacturing as the object is formed from additive layering of material on top of material. This was traditionally done with a 3D printer, using polymer as the material, but in the recent years, different applications of 3D printing have allowed expansion to different materials, such as epoxy resins, titanium, steel, and wax.[10]

CURRENT APPLICATIONS

3D imaging has rapidly made its advent in multiple specialties of medical practice, including orthopedic surgery, neurovascular surgery, forensic pathology, pathology, and dentistry. It has also made an impact in medical and allied health education.

Orthopedic surgery

3D images of bones are reconstructed from a CT or MRI, and a prototype of the bone is printed via layered manufacturing technique for surgical implantation. In addition, the prototype of the bone allows the surgeon to familiarize themselves with the procedure prior to execution. Prosthetics are also being produced with 3D imaging, modeling, and printing. With these technologies, the prosthesis can be customized to the specific needs of the patient.[11] As 3D printers are becoming widely available, they are no longer an expensive product. Customizing prostheses for patients is more cost effective as it allows for a more detailed fit, shorter surgical duration and uneventful recovery time. 3D printing of the patients' bones is patient specific and enables physicians to construct prosthetics that are tailored to meet the patient's surgical needs, in terms of shape, size and unique anatomy (Figure 2).

FIGURE 2.
Human Femur – Exterior scan of human left femur bone

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Neurovascular surgery

Pre-surgical 3D imaging and modeling of the neurovascular abnormality can allow the surgeon to not only diagnose but also plan the surgical procedure. Sullivan *et al*. describes a case report in which an eight-year-old boy was treated for a fusiform aneurysm of the left internal carotid artery. Due to the complexity of the anatomy, the neurosurgeons needed a 3D model of the patient's arteries in order to develop a surgical plan. The patient's cerebral vasculature was 3D printed with silicone using the technology, Vascular Simulations, and the surgical plan was rehearsed through simulations. An image of the silicone 3D model is shown in Figure 3. The arrow is pointing to an aneurysm in the ICA and the arrow head is pointing to a kink in the wall of the MCA. Without 3D technology, the surgery would have taken longer, with longer period of general anesthesia, and with increased risk for error due to poor visualization of the patient's unique vascular anatomy.

FIGURE 3.
Image of the silicone 3D model

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Forensics

With 3D imaging, forensic investigation can map entire crime scenes and reconstruct 3D models of evidence such as bones, teeth, and fingerprints. During a crime investigation, the teeth of victims are often displaced in the midst of a disaster or accident. Digital tooth reconstruction can be used to 3D print a tooth with the information given by the intra-alveolar morphology of the tooth socket.[13] A study by Johnson *et al*. has shown that there are minimal errors in the reconstruction of the 3D printed tooth. This enhances the victim identification process in forensic investigations even in the absence of teeth.[13] Depicted in Figure 4 is a

3D model of a 1st molar, tooth "3" according to the Dental Numbering System. Evidence of human remains, such as teeth, found at crime scenes can be reconstructed to produce models like the one shown.

Orthodontic

3D imaging has allowed for a realistic visualization of the craniofacial and dentofacial anatomy. The detailed 3D images show depth, spatial accuracy, and soft tissues that were not previously visualized using 2D images.[14] Surgical correction of orofacial deformities such as cleft lip palate (CLP) can be a challenging procedure due to the complex distortion of many anatomical structures, which affects approximately 7,000 infants in the US annually.[15] With the use of Cone Beam CT (CBCT), the orthodontist is able to successfully treat CLP. It also allows them to see if the airway and oral structures are affected by the pathological process.[14] With CBCT, orthodontists are able to effectively plan their surgical procedures and develop bone grafts to treat CLP patients, successfully restoring normal speech and feeding functions.

FIGURE 4.
3D model of 1st molar

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Pathology

Though light microscopy is the current gold standard for tissue specimen analysis, there are many drawbacks to its use. It can be destructive to the tissue specimen, distort the tissue morphology, limit the potential to analyze the tissue's microenvironment, and can be very time consuming[16,17,18.] 3D imaging technologies such as special tissue clearing techniques, laser scanners, whole slide imaging, file formats, and 3D reconstructions of tissue specimens have become powerful assets for pathologists in extending their knowledge and understanding of histopathology.[19]

A study from the Osaka University, Graduate School of Medicine, focused on the use of 3D confocal scanning microscopy with a tissue clearing technique called clear unobstructed brain imaging cocktail and computational analysis (CUBIC).[20] CUBIC tissue clearing technique is useful in enhancing the transparency of the tissue specimens. Confocal scanning microscopy is a customized light microscopy which increases the depth and resolution of the tissue specimen in a three-dimensional view.[19] The combinations of these two techniques provided a more sensitive visualization of the tissue specimens, such that they were able to identify microscopic metastatic lesions in the lymph nodes, previously missed by conventional light microscopy.[20] Tolkach *et al*. explored the use of 3D reconstruction technology on prostate adenocarcinoma specimens and its morphology.[16] Reconstruction technology uses laser scanners to algorithmically reconstruct the specimen tissue forming a three-dimensional image.[19] 3D reconstruction can help with evaluating the grading score, direction of tumor growth, invasive pattern of tumor, and patient prognosis.[16] 3D imaging technologies can also be used for educational purposes in pathology, enhancing the learning process for students and residents.

Medical and allied health education

The application of 3D imaging technologies has not only transformed our clinical knowledge in the healthcare field, but it has also become an important teaching aid. Medical students benefit from this technology as 3D anatomical atlases of the human body have been incorporated into the medical education, allowing students to better understand spatial anatomy.[21] A randomized control study at Yuying Children's Hospital of Wenzhou Medical University, showed that 3D printed models were beneficial in helping students understand complex anatomical sites.[22] It has also become a crucial training technology for surgical residents. A study using 3D imaging to stimulate a virtual reality (VR), allowed surgical residents to practice their surgical skills. The study found VR training to be helpful for surgical residents practicing procedures.[23] In addition, nursing education has also implemented 3D imaging technologies as a way of improving care for their patients. Results from a study showed 3D imaging models of complex congenital heart diseases (CHD) were used to help nurses better nderstand cardiac anomalies.[24]

FIGURE 5.
Interactive 3D image of a hysterectomy specimen with a leiomyoma.

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FUTURE APPLICATIONS

Given the ability to duplicate the radiologic abnormalities, 3D imaging has already served as a useful tool in many fields as discussed above. In the future, this technology will continue to advance radiology by increasing the diagnostic sensitivity. Given 3D technology can be used to image and print complex structural anomalies, such as valvular, and congenital disorders, it will be beneficial in depicting the patient's heart for custom implants and devices.[25] The incorporation of 3D imaging technologies in surgery will continue to benefit the healthcare system financially and improve surgical outcomes for patients. With the reduction in surgery time and postoperative complications, studies showed 3D imaging has helped reduce operating room cost ranging from $1488-$3720 per surgical case.[26] 3D imaging technologies such as handheld intraoral scanners will allow dentists to have a quick and precise image of dental anatomy.[27] The images will be used to print 3D models of orthodontic splints, night guards, and aligners, all without having to make a physical mold out alginate, a current practice seen traditionally.[28]

CONCLUSION

3D imaging has become a major advancement in health technologies and has shaped the health field in clinical diagnosis, treatment options, customized patient care, and health education. It is a foundation in many diagnostic procedures such as evaluating intracranial aneurysm and staging cancers. In addition, 3D imaging has made a substantial impact on treatment options for clinicians and their patients. It has helped clinicians save lives in a variety of disease entities, including valvular heart defects and congenital malformations. The technology has also benefited patients by receiving meaningful, personalized care, such as customized prostheses, thereby streamlining the surgical procedure and the postoperative progress. Furthermore, 3D imaging technologies can help decrease health care costs due to its efficient diagnostic procedures, shorter surgical duration, and effective treatment plans. In academia, 3D imaging has been used in numerous health professions to further educate medical students, nurses, and surgeons. In conclusion, 3D imaging has revolutionized medicine and its continual development will rapidly become a mainstay in diagnostics and treatments in health care.

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AUTHOR DISCLOSURES:

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Update on Hypertension and Adaptations for Treatment

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ABSTRACT

Hypertension (HTN) affects 46% of the US adult population and plays a major role in cardiovascular disease (CVD). Approximately, there were 90,098 deaths in 2017 primarily attributed to high blood pressure (BP). Recent guidelines recommend screening all adults for HTN. Management of elevated BP substantially reduces the risk of heart failure, stroke and myocardial infarction. Recommended lifestyle modifications include weight loss for overweight or obese patients, regular exercise, the dietary approached to stop hypertension (DASH) diet, reduced dietary sodium intake, and reduced alcohol intake. Most HTN patients will need at least 2 drugs to control BP. Current guidelines from the ACC and AHA state that a BP level goal of < 130/80mmHg for adults with confirmed HTN and with out additional markers of increased atherosclerotic cardiovascular disease (ASCVD) risk may be acceptable.

BACKGROUND

Hypertension (HTN) is one of the most important preventable contributors to disease and death in the U.S., resulting in myocardial infarction (MI), stroke, and renal failure if it is not detected early and treated appropriately.[1] Starting at a blood pressure of 115/75 mm Hg, every increase of 20 mm Hg in systolic blood pressure (SBP) and/or increase of 10 mm Hg in diastolic blood pressure (DBP) is associated with a doubling of the risk of death from stroke, heart disease, or other vascular disease.[2] HTN is largely managed with drug therapy, clinical pharmacists often participate in management, especially, to manage HTN along with risk factors. This book chapter will emphasize the new recommendations for BP management and will focus on the pharmacotherapy of HTN.

The prevalence of HTN in U.S. adults has continued to increase with age (Table 1). The American College of Cardiology and American Heart Association (ACC/AHA) 2017 blood pressure guidelines lowered the threshold for the diagnosis of HTN to 130/80 mm Hg, which led to a new HTN prevalence of 46% of U.S. adults. HTN is more prevalent in blacks in both men (59%) and women (56%) followed by white (47%) in men and 41% in women).[3]

OUTCOME STUDIES ON ANTI-HYPERTENSIVE THERAPY

SBP begins to rise steadily at about age 45 and continues throughout life. In contrast, DBP rises until about age 55, then decreases steadily.[5] For every 2 mm increase in Systolic Blood Pressure (SBP),

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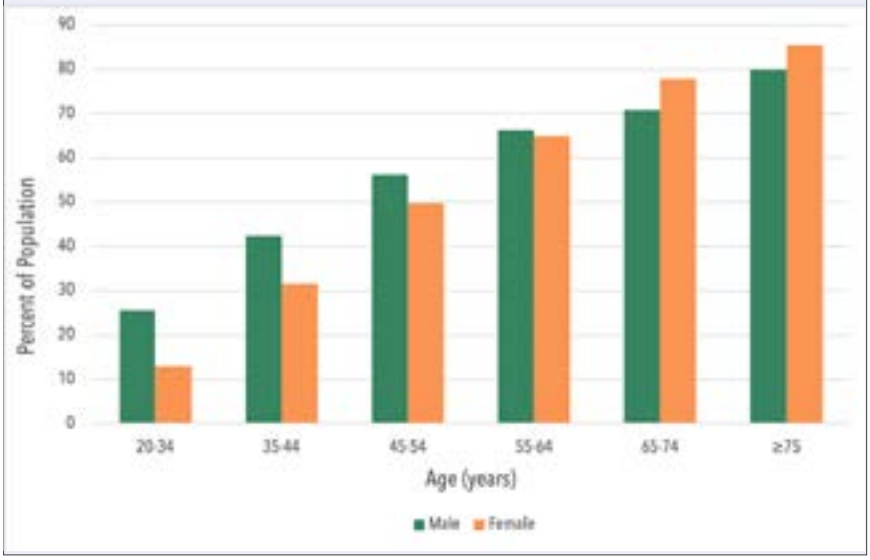
risk of fatal stroke increases by 7% and coronary heart disease by 5%, as suggested by a large observational study. SBP must be closely monitored throughout life and evaluating DBP alone will result in underestimation of cardiovascular (CV) risk.[6]

TABLE 1.



Thiazide-like diuretic and ß-blockers

In 1991, *Systolic Hypertension in the Elderly Program (SHEP)* demonstrated the effect of antihypertensive therapy in older patients with elevated SBP significantly reduced the risk of stroke. 4736 patients were randomized to active treatment (n=2365) with chlorthalidone with the addition of atenolol based on blood pressure response, or to placebo (n=2371). The five-year incidence of total stroke was 5.2 per 100 participants with active (average BP= 143/68mmHg) treatment compared with placebo (average BP= 155/72mmHg) 8.2 per 100 participants (P=.0003).[7] Relative risk reduction of nonfatal MI plus coronary death (0.73), major cardiovascular events (0.68) and death from all causes (0.87) in the patients who received antihypertensive therapy. *Medical Research Council (MRC)* study reported 19% reduction of cardiovascular events ($p < 0.05$) and 45% of strokes in patients who were randomized to propranolol or thiazide compared to placebo.[7] Furthermore, *Swedish Trial in Old Patients with Hypertension (Stop-Hypertension)* have shown the 38% reduction in combined stroke and MI (p=0.003) with 45% reduction in stroke alone (p=0.008) in patients who were treated with ß-blockers and one diuretic compared to placebo.[9]

Badve *et al.'s.*[10] meta-analysis described that ß-blockers lowers the risk of all-cause and cardiovascular mortality in patients with Chronic Kidney Disease (CKD) and systolic heart failure.[11] ß-blockers are effective in broad range of CKD Patients who are post-MI. Abbott *et al.*[11] reported that the ß- blockers lowered the risk of heart failure (HR 0.69, 95% CI 0.52-0.91, p=0.008) and cardiac death on dialysis patients from the US Renal Data System (USRDS).

Angiotensin-converting enzyme inhibition (ACEI) and Calcium channel blocker (CCB)

Heart Outcomes Prevention Evaluation (HOPE) study was stopped early because of convincing evidence of the benefit of ramipril treatment on the cardiovascular death, non-fatal MI and non-fatal stroke (14% vs. 17.8% on ramipril and placebo, respectively; relative risk reduction 22%, p<0.001). This study reported a risk reduction of 32% for stroke, 20% for MI, 26% for cardiovascular death and 16% for all-cause mortality, as well as a reduction in the risk of several other endpoints including heart failure and revascularization procedures.[12]

In 1999, *Systolic Hypertension in the Europe (Syst-Eur)* investigated the effect of nitrendipine with the possible addition of enalapril and hydrochlorothiazide to reduce the cardiovascular complications in older patients with elevated SBP of 160-219 mmHg. The total rate of stroke was reduced by 42% (P=.003) and of nonfatal stroke by 44% (P=.007), as well as all cardiac endpoints, including sudden death (26%; P=.03). Nonfatal cardiac endpoints decreased by 33% (P=.03) and all fatal and nonfatal cardiovascular endpoints by 31% (P<.001). Cardiovascular mortality was slightly lower (27%) in the patients who received antihypertensive therapy (P=.07), but all-cause mortality was not significantly decreased (14%; P=.22).

The *Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)* was designed to determine whether the occurrence of fatal coronary heart disease (CHD) or nonfatal MI is lower for high-risk hypertensive patients treated with NORVASC (CCB), lisinopril (ACEI), or doxazosin (ß-adrenergic blocker), compared with chlorthalidone (diuretic treatment). At the initial visit, the proportion of participants at or below the BP goal (<140/90 mm Hg) was 26-28%; at five years, it was 68%, 66%, and 61% for the chlorthalidone, amlodipine, and lisinopril groups, respectively. No significant difference was observed between the relative risk (RR) of Fatal CHD and

nonfatal MI for amlodipine compared to chlorthalidone (RR=0.98; 95% CI 0.90-1.07) and between lisinopril and chlorthalidone (RR= 0.99, with a 95% CI 0.91-1.08).[13] The Lisinopril group had a 15% higher risk for stroke. Based on these study results chlorthalidone was superior to lisinopril and doxazosin in preventing aggregate CV events, principally stroke, heart failure, angina, and coronary revascularization and no difference for stroke between the amlodipine and chlorthalidone groups. The three core messages for the ALLHAT antihypertensive trial are:

1. Diuretics should be the drug of choice for first step therapy of HTN.
2. For the patient who cannot take a diuretic (which should be an unusual circumstance), CCB's and ACEI's may be considered.
3. Most HTN patients require more than one drug. Diuretics should generally be part of the antihypertensive regimen. Lifestyle advice should also be provided.

The *Anglo - Scandinavian Cardiac Outcomes Trial: Blood Pressure-Lowering Arm - ASCOT-BPLA* evaluated whether CCB with or without an ACEI is more effective than an older regimen of ß-blocker with or without a diuretic and whether it reduces coronary heart disease (CHD) events in hypertensive patients with relatively low cholesterol levels. The trial was discontinued early due to efficacy in the amlodipine/perindopril group and concerns regarding the patients in the atenolol/ bendroflumethiazide group. The reduction in the primary endpoint of nonfatal MI and fatal CHD was not significant in amlodipine/perindopril group (HR 0.90, 95% CI 0.79-1.02, p = 0.1052). However, several prespecified secondary endpoints were significantly lower

TABLE 2.
Best proven nonpharmacological interventions for the prevention and treatment of hypertension[17]

	NONPHARMACOLOGICAL INTERVENTION	GOAL	APPROXIMATE IMPACT ON SBP	
			HYPERTENSION	NORMOTENSION
WEIGHT LOSS	Weight/body fat	Best goal is ideal body weight but aim for at least a 1-kg reduction in body weight for most adults who are overweight. Expect about 1 mm Hg for every 1-kg reduction in body weight.	-5 mm Hg	-2/3 mm Hg
HEALTHY DIET	DASH dietary pattern	Consume a diet rich in fruits, vegetables, whole grains, and low-fat dairy products, with reduced content of saturated and total fat.	-11 mm Hg	-3 mm Hg
REDUCED INTAKE OF DIETARY SODIUM	Dietary sodium	Optimal goal is <1500 mg/d but aim for at least a 1000-mg/d reduction in most adults.	-5/6 mm Hg	-2/3 mm Hg
ENHANCED INTAKE OF DIETARY POTASSIUM	Dietary potassium	Aim for 3500–5000 mg/d, preferably by consumption of a diet rich in potassium.	-4/5 mm Hg	-2 mm Hg
PHYSICAL ACTIVITY	Aerobic	→ 90–150 min/wk → 65%–75% heart rate reserve	-5/8 MM HG	-2/4 mm Hg
	Dynamic resistance	→ 90–150 min/wk → 50%–80% 1 rep maximum → 6 exercises, 3 sets/exercise, 10 repetitions/set	-4 MM HG	-2 mm Hg
	Isometric resistance	→ 4 × 2 min (hand grip),1 min rest between exercises, 30%–40% maximum voluntary contraction, 3 sessions/wk → 8-10 wk	-5 MM HG	-4 mm Hg
MODERATION IN ALCOHOL INTAKE	Alcohol consumption	In individuals who drink alcohol, reduce alcohol to: → Men: ≤2 drinks daily → Women: ≤1 drink daily	-4 MM HG	-3 mm Hg

in the amlodipine/perindopril group, including all-cause mortality (HR 0.89, 95% CI 0.81-0.99, p = 0.025), all coronary events (HR 0.87, 95% CI 0.79-0.96, p = 0.007), all cardiovascular events and procedures(HR0.84,95%CI0.78-0.90,p< 0.0001),stroke(HR0.77,95%CI0.66-0.89, p = 0.0003), and cardiovascular mortality (HR0.76,95%CI0.65-0.90,p=0.001).[14]

ANGIOTENSIN RECEPTOR BLOCKER (ARB)

The *Valsartan Antihypertensive Long-Term Use Evaluation (VALUE)* Trial showed that amlodipine significantly reduced both systolic and diastolic BP compared with valsartan throughout the six-year duration of the trial. The amlodipine arm showed significantly fewer MIs than the valsartan arm (P=0.02 and HR=1.19; valsartan had 19% excess risk of MI). The rates of stroke were similar between the 2 arms (P=0.08). There was a statistically significant decrease of stroke in the amlodipine arm in the first three months of the trial and a trend favoring amlodipine remained until the end of the trial (non- significant).[15]

The *Systolic Blood Pressure Intervention Trial (SPRINT)* compared the safety and efficacy of intensive lowering of SBP to <120 mm Hg versus routine management to <140 mm Hg and were followed-up for over 5 years. The trial was terminated early due to overwhelming evidence of benefit. The primary outcome, MI, acute coronary syndrome (ACS), stroke, congestive heart failure (CHF), or CV death, was significantly lowered in the intensive BP management arm compared with the routine management arm (5.2% vs. 6.8%, HR 0.75, 95% CI 0.64–0.89; p < 0.0001).[16]

PREVENTION

The most important way to prevent CV risk in hypertensive is to promote a healthy lifestyle throughout the life. All adults should consume a healthy diet with consumption of fruits, vegetables, whole grains, fish and low-fat dairy products with reduced intake of alcohol, trans fats, red meat, carbohydrates and sweetened beverages. Counseling and caloric restriction are recommended for achieving and maintaining weight loss in overweight and obese individuals.

TABLE 3.
Compelling indications for individual for BP management[19]

	DIURETIC	ß-BLOCKER	ACEI	ARB	CCB	ALDOSTERONE ANTAGONIST
CHF	•	•	•	•		•
POST-MI		•	•			•
CAD-RISK	•	•	•			
DIABETES MELLITUS	•	•	•	•	•	
RENAL DISEASE				•	•	
RECURRENT STROKE PREVENTION	•		•			

Abbreviations: CHF, congestive heart failure; MI, myocardial infarction; CAD, coronary artery disease; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCB, calcium channel blocker

The seventh report of the Joint National Committee (JNC VII) on prevention, detection, evaluation, and treatment of high BP reported that thiazide-like diuretics are effective and relatively safe for the management of uncomplicated HTN.[18] HTN may exist in association with other conditions in which there are compelling indications for BP management (Table 3). Therapeutic decisions should be aimed at both the compelling indication and lowering BP. Diabetics and CKD patients will require more than two medications to achieve goal BP.

In 2014, JNC VIII guidelines for the management of HTN in adults announced that the initial anti-hypertensive treatment should include a thiazide diuretic, calcium channel blocker, ACEI, or angiotensin receptor blocker (ARB) in general non-black population where as in general black population the initial treatment should include a thiazide diuretic or calcium channel blocker, including those with diabetes. Blood pressure should be monitored, and the treatment regimen adjusted until the target blood pressure is reached. If the target BP is not achieved within one month after initiating therapy, increase the dosage of the initial medication or second medication should be added from the drug classes listed above (do not combine an ACEI with an ARB). A third drug should be added if necessary; Antihypertensive drugs from other classes can be used (e.g., beta blockers, aldosterone antagonists) if the target BP is not achieved using only the above drug classes listed.[20] Adults with CKD and hypertension should receive

an ACE inhibitor or ARB as initial or add-on therapy, based on moderate evidence that these medications improve kidney-related outcomes in these patients.

In addition to recent published guidelines recommending a total risk approach for reducing the risk of CV events, the recent British Hypertension Society (BHS)/ National Institute for Health and Care Excellence (NICE)[22,23] guidelines for HTN is also changing the recommended choices of drug therapy based on recent clinical trials.

The essential effect of ACEIs on the angiotensin aldosterone system (RAAS) is to block the conversion of the relatively inactive angiotensin I (Ang I) to the active Ang II. Angiotensin II receptor blockers (ARBs) bind to the AT1 receptor with high affinity. All agents that inhibit the RAAS, including renin inhibitors, suppress the negative feedback loop, leading to a compensatory rise in plasma renin concentration. When this rise occurs during treatment with ACEIs and ARBs, the result is increased plasma renin activity (PRA). Studies have shown that antihypertensive agents that target the renin-angiotensin system prevent kidney decline better, even when achieving similar BP goals.[26] These results were found primarily in patients with proteinuria, whereas the benefit was less substantial for those without proteinuria. Based on these findings, guidelines recommend ACEIs or ARB therapy as first-line treatment for those with diabetes or those presenting with nondiabetic kidney disease, HTN, and proteinuria. Data indicate that ACEIs and ARBs are equally effective in lowering BP and reducing proteinuria.[27] A recent meta-analysis suggests that ACEI therapy may provide superior benefit over ARB therapy for the treatment of HTN due to a 10% reduction in all-cause mortality.[28] These results were determined for patients with HTN and did not apply to patients with additional comorbidities such as CKD. Therefore, selection of one agent over another will depend on patient-specific factors such as potential for side effects and cost. Treatment with both an ACE inhibitor and an ARB is not recommended, as this combination has been shown to worsen kidney function. Combination ACE inhibitor and ARB therapy did not reduce cardiovascular mortality or morbidity in comparison to monotherapy of an ACE inhibitor. [27, 28]

TABLE 4.
Joint National Committee (JNC) VII vs VIII: Drug Therapy[19]

JNC VII	JNC VIII
RECOMMENDED → 5 classes to be considered as initial therapy → Thiazide-type diuretics as initial therapy for most patients without compelling indication for another class → Included a dual dose range of antihypertensive medications Specified antihypertensive medication classes for most patients without compelling indications such as diabetes, CKD, heart failure, myocardial infarction, stroke and high CVD risk.	**RECOMMENDED** → 4 specific medication classes to be considered as initial therapy → ACEI/ARB, CCB or Thiazide-type diuretic as initial therapy for most patients → Doses based on randomized clinical trial (RCT) evidence Specified medication classes based on evidence review for racial, CKD, and diabetic subgroups.

TABLE 5.
BHS/NICE guidelines recommendations for combining antihypertensive drugs[24, 25]

	AGE <55 YR AND NON-BLACK	AGE >55 YR OR BLACK
STEP 1	A (ACEI or ARB)	C (CCB) or D (Diuretic)
STEP 2	A +	C or D
STEP 3	A +	C or D
STEP 4 RESISTANT HYPERTENSION	Add either α-Blocker or loop diuretics/spironolactone or ß-Blocker	

A: Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB)

C: Calcium channel blocker (CCB)

D: Thiazide diuretic

The BP thresholds and recommendation treatment according to 2019 ACC/AHA prevention Guidelines as shown in Figure 1.[29] The patients with diabetes/ CKD are automatically classified in the high-risk category. For stage 2 hypertension 2 antihypertensive agents of different classes need to be consider for initiation of therapy and should be closely monitored.

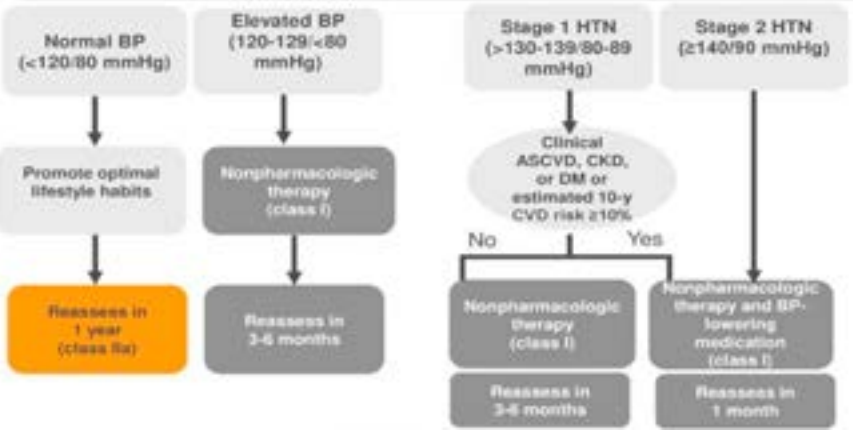
Renal sympathetic denervation (RDN) is being actively investigated as a novel treatment modality for patients with HTN.

Pivotal trials for renal denervation (RDN) for uncontrolled HTN using radiofrequency ablation in the main renal arteries showed that RDN was effective in lowering blood pressure (BP) of 15-20mm Hg.[30] Recent data, from meta-analysis, suggest that the BP lowering effect of RDN, even if smaller than initially anticipated, is similar to that observed with many currently approved antihypertensive drugs. Nevertheless, many questions remain about RDN, including its long-term safety and effectiveness, and how it might be integrated into the treatment for HTN.

To determine the appropriateness of pharmacological therapy after quantitative risk estimation in cases that are unclear, selective use of a coronary artery calcium (CAC) measurement can inform decision-making for cholesterol-lowering or antihypertensive medication use in intermediate-risk individuals. Coronary artery calcium (CAC) score is a direct measure of subclinical atherosclerosis.[31]

FIGURE 1.

Blood Thresholds and Recommendations for Treatment and Follow-Up[17]



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Malaria Trophozoite

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A 71-year-old man living in El Salvador developed anemia, indirect bilirubinemia and intermittent fever for the past several months. Ultrasound of the abdomen revealed mild splenomegaly. Both thick and thin blood smears for malaria failed to show malaria species.

A peripheral blood smear of Giemsa stain was sent to my clinic for review. The slide showed RBCs with ring form trophozoite of malaria (Figure 1, 2). It is most likely plasmodium vivax as the size of ring is bigger than that of p. falciparum and p. vivax is the most common malaria species in El Salvador.[1]

The patient was treated with anti-malaria medicine. The hemolytic anemia improved markedly and he is now symptom free.

FIGURE 1.
Slide showing RBCs with ring form trophozoite of malaria

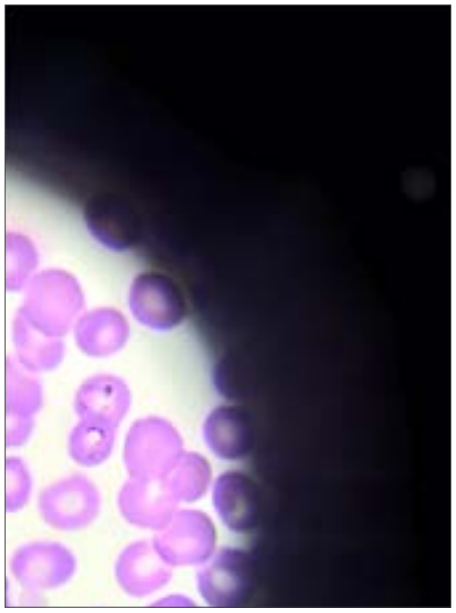
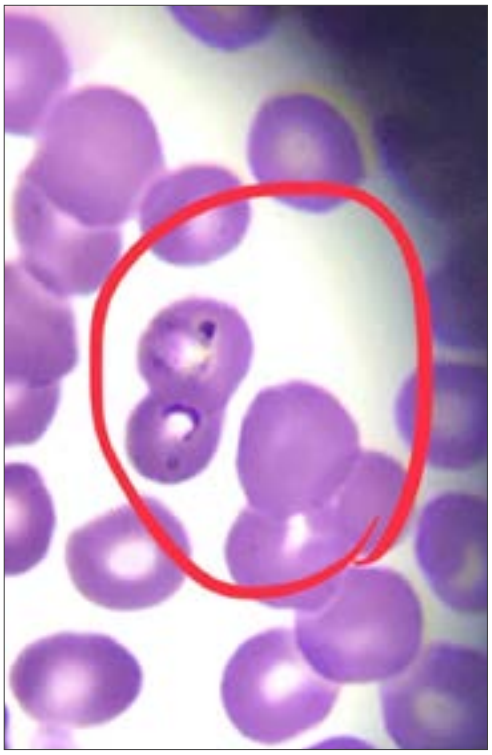


FIGURE 2.
Slide showing RBCs with ring form trophozoite of malaria



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Physician's Role in Preventing Controlled Substance Diversion

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KEYWORDS:

Controlled Substance, Opioids, Pain Management, Substance Diversion

ABSTRACT

Diversion of opioids and other controlled substances for personal use by physicians poses a risk to patient health, safety and welfare, as well as the health and well-being of the physicians themselves. This article reviews the problem of controlled-substances diversion by physicians and their role in prevention.

INTRODUCTION

Controlled substance diversion is defined as the illegal distribution or abuse of prescription drugs for unintended purposes by staff or patients, and it puts physicians at regulatory and legal risks.[1] According to The Centers for Medicare and Medicaid Services (CMS) report, *Partners in Integrity*, "physicians and other prescribers often have the first opportunity to identify, control, and report drug diversion."[2]

PRACTITIONER LAWS AND REGULATIONS

The Drug Enforcement Agency (DEA) provides the following guidelines to aid practitioners in appropriately prescribing, administering and dispensing controlled substances. These guidelines are intended to educate physicians of their responsibilities in safeguarding the diversion of controlled substances:

§1306.04 Purpose of issue of prescription.

1. To be valid, a prescription for a controlled substance must be issued for a legitimate medical purpose by an individual practitioner acting in the usual course of his professional practice.[3]
2. The responsibility for the proper prescribing and dispensing of controlled substances is upon the prescribing practitioner, but a corresponding responsibility rests with the pharmacist who fills the prescription. Pharmacists are not obligated to fill the prescription.[3]
3. Practitioners shall provide controls and procedures to guard against the diversion of controlled substances.[3]

According to the Controlled Substances Act, physicians can administer, prescribe, or dispense a controlled substance if there is a legitimate medical purpose, and it is done within the usual course

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of professional practice.[4] The National Institute of Drug Abuse and the DEA identify the top five prescription drugs with the highest potential for diversion and abuse as anabolic steroids, central nervous system depressants, hallucinogens, opioids, and stimulants.

The usual course of professional practice mentioned in the first purpose above is defined as documentation by the practitioner of the patient's medical complaint, the patient's medical history, and by conducting a medical examination. A legitimate medical purpose must be validated by the complaint, history, and examination before a controlled substance should be prescribed.

In the case of opioids, some physicians refuse to treat patients who need these medications to function on a daily basis. For the physicians who do provide care to pain patients and prescribe controlled substances, they need to know how to recognize the signs of controlled substance diversion and prevent it in their practice.

TABLE 1.
Physician/Practice Diversion Red Flags[5]

	Are state laws followed when prescribing controlled substances?
	Multiple drugs prescribed within the same drug category
	Patients travel long distances to see this physician
	Excessive quantities of controlled substances prescribed relative to the medical condition being treated
	Ignoring signs of patient abuse such as under the influence
	Starting patient on high dose
	Continued prescribing even though ineffective for treatment purposes
	Only treat patients with narcotic controlled substances
	Allowing non-medical staff to determine narcotic prescribed – physician just signs the prescription
	Coaching patients on what to say to get the narcotics they want
	Violations of own pain management policies and guidelines
	Ignore warnings from insurance companies, law enforcement, other physicians
	Receiving other compensation for narcotic prescriptions such as sex, guns or drugs
	Patient deaths
	Ignoring toxicology reports

RECOGNIZING DRUG DIVERSION IN YOUR PRACTICE

There are several signs of controlled substance diversion, and while physicians should approach their patients with trust, they must be aware that patients can be deceptive. Attention must also be paid to employees, other physicians, friends, and family members.

The DEA recommends looking out for the following physician/practice drug diversion red flags in Table 1.

RECOGNIZING DRUG DIVERSION IN YOUR PATIENTS

A patient encounter isn't adding up. They are claiming to be traveling through town on business or visiting relatives and also requesting an appointment toward the end of the day or after traditional office hours. One common ploy drug diverter's use is to ask to be seen immediately or to be given a prescription right away because they have to "catch a plane" or "get to an important appointment."[6] They may claim that they have lost a paper prescription, forgotten to pack their medication, or had their medication stolen.[6]

When patients appear to be extremely well-informed about specific medications and sound like they are reading from a textbook or on the opposite end of the spectrum, mispronouncing drug names to come across as unfamiliar with the controlled substance, proceed with caution and a heightened awareness of other red flags. Another tactic used is posing as government officials or pharmaceutical company representatives. The DEA recommends looking out for the following patient diversion red flags in Table 2.

BEST PRACTICES TO REDUCE RISK

As a practitioner, your role in the proper prescribing, administering, and dispensing of controlled substances is critical to the patient's health and to safeguard society against the diversion of controlled substances.[6] A comprehensive approach to risk reduction includes taking precautions to minimize controlled substance diversion.

For patients who use or request a combination of prescriptions to achieve an enhanced effect, proceed with caution and do your due diligence. Patients with extensive pain management might need to be referred to specialized pain practices.[7] Be sure to extensively document your rationale when prescribing or choosing not to prescribe a controlled substance.[7] Your DEA or license number needs to be kept secure as to ensure confidentiality (unless disclosure is required.)[7] If paper prescriptions are being utilized, move to electronic prescribing as this helps eliminate the theft of prescription pads. Staff education on prescription policies and how to recognize common warning signs of patient drug diversion needs to held regularly along with creating a workplace environment where open communication and compliance are prioritized.[7]

Check to see if there is a State Prescription Drug Monitoring Program in your state and, if possible, start utilizing this resource. Collaborate with pharmacy benefit managers and managed care plans to determine the medical necessity of prescriptions for controlled substances.[7]

FIGURE 1.

CMS. gov infographic outlining drug diversion and potential consequences for healthcare workers.[11]

TABLE 2.

Patient Diversion Red Flags[5]

⚑	Refuse medical exam
⚑	Brief initial office visits or follow-ups
⚑	Unwilling to give permission to access past medical records or allow contact with previous providers
⚑	Claim they cannot precisely remember where they were last treated or that the previous clinic
⚑	Patients leave the office suddenly if things are not going their way
⚑	Unusually high (or low) understanding of medications
⚑	Diverters may exaggerate or feign symptoms
⚑	Specific drug requests – Asking for controlled substances they want
⚑	Doctor shopping

Unused prescription medications and pharmaceutical samples need to be properly disposed. The DEA recommends that physicians initially contact their pharmaceutical sales representatives as many will take back their samples for proper disposal. If the manufacturing company refuses to take back the samples, physicians can contact special authorized collectors known as "reverse distributors." These companies are registered to take all types of drugs back from physicians for the purpose of proper destruction.[8]

For unused prescription medications, physicians and patients can search the DEA's Office of Diversion Control's website database that keeps an updated searchable database of facilities.[9] Another option is the National Association of Boards of Pharmacy locator tool.[10] This tool is for patients to check for government entities in their area that have a drug drop box. It should be mandatory to take unused medications to a licensed entity or appropriate government agency for proper disposal in order to minimize any opportunity for controlled substance diversion.

Controlled substances are one of a variety of options for physicians to form the basis of a treatment plan for patients with chronic pain. Each patient is different, and treatment depends on complex factors. Physicians need a regimented and evidenced-based approach to the use of controlled substances in their practice of medicine, as they are both the solution and the problem.

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Introduction and Follow Up of Ongoing WiRED International Program

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ABSTRACT

As we write this article, the expanding coronavirus pandemic has crushed healthcare systems around the world. Increasingly, ministries of health, non-governmental organizations and hospitals are turning to their reserve workforces — retired professionals, medical and nursing students, and community health workers (CHWs). In under-resourced regions, where the options are limited, they are reaching out to these CHWs, a quasi-professional corps of people who play a critical role in the last mile of many health systems. This trained force delivers basic health services, provides community members with health and prevention information, and becomes the eyes and ears for the official healthcare systems. The need for CHWs has surged along with the onset of the coronavirus, but CHWs, like everyone in the healthcare system, are in short supply. The CHW training program that we describe in this paper started out with a different set of motivations and a very different timetable. The coronavirus crisis has imposed changes on our training protocols and greatly accelerated the need for CHWs in all regions, but especially, underserved regions. In this paper we describe our plans and approaches developed in a very different global environment. At the end, we speculate about how this program will unfold now that training procedures must change, and how CHWs have become ever more important in community health.

INTRODUCTION

Physician density varies widely among countries, with around 500 doctors per 100,000 people at the high end and three per 100,000 at the low end.[1] Although the ratios don't line up neatly with gross domestic product, the lowest physician counts are usually in the poorest regions of Africa, parts of the Middle East and South Asia and segments of Latin America.[2] With doctors and nurses absent or scarce, common people are left alone to heal the sick, deliver children, address chronic illnesses, all with skills uninformed by the latest medical practices. Moreover, many communities know little about methods of prevention to stave off illnesses.

The number of doctors in low-resource regions is unlikely to grow anytime soon,[2] and that is where the World Health Organization (WHO) sees CHWs entering the picture, not as substitutes for qualified physicians, but as supplements offering basic clinical services, referrals, health training, and links to the larger healthcare system. CHW services are wide and varied and differ from place to place. A lingering problem has been how to train CHWs with a standard curriculum while adapting to local differences in health conditions, cultural norms, government requirements and resource availability.

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WHO EXPECTATIONS FOR CHWS

WiRED International has been working on health education in underserved regions since the late 1990s, and during these past two decades, we have observed the many gaps in health delivery systems that give rise to the need for CHWs. Physicians and medical facilities throughout low-resource communities are in short supply, breathtakingly so in places we have worked in Africa, Latin America, Eurasia, conflict regions of the Middle East, and in earlier years in countries of the former Yugoslavia. We've observed how communities alarmingly are as unprepared for infectious disease outbreaks as they are for routine prevention and management of non-communicable illnesses.

Beyond severe gaps in prevention and medical services, the broken link between official health agencies and dislocated populations may be one of the most perilous and little discussed shortfalls in fragile health systems. Such communities often are isolated economically and geographically from the formal healthcare system, and this separation suppresses the flow of critical information in both directions — to and from the healthcare system and the communities. As a consequence, information about disease prevention and preparedness is slow to diffuse to isolated communities, if the information gets there at all. Moreover, reports about unhealthy conditions within isolated communities often fail to reach outside health agencies. This, of course, has wider population implications beyond the affected communities, when infectious diseases yield dangerous consequences that could have been stemmed with good communication and early interventions. So, broken links between disenfranchised communities and the larger health system have negative consequences for all.

We have been well aware of WHO's convincing arguments in favor of developing a quasi-professional corps of workers who could play a critical role in the health system. This trained force would deliver basic health services, but they would not be physicians. They would provide community members with health and prevention information, but they would not be professional medical educators. They would be the eyes and ears for the official health systems, but they would not be health inspectors. CHWs, thus, provide a range of critical services without the intense focus expected of specialists in medicine, teaching and assessment.

CHW IN-PERSON TRAINING PROGRAM

Specifically, WHO has offered these qualifications, functions and expectations for CHWs:[3]

- CHWs can make a valuable contribution to community development and, more specifically, can improve communities with basic health services.
- CHWs teach communities about health and sanitation and stress prevention.
- CHWs observe populations and local environments, watching for unhealthy and threatening conditions.
- CHWs can take actions that lead to improved health for everyone and especially for the health of children.
- CHW programs must include continuing health education. Ongoing training ensures that CHWs remain current in health topics and connected to the health system.
- To be able to make an effective contribution, CHWs must be carefully selected, appropriately trained and — very important — adequately and continually supported.
- CHWs must be firmly embedded in the communities they serve.
- CHW programs succeed in communities that actively want them.
- CHWs must respond to local cultural norms and customs to ensure community acceptance and ownership.
- Examples of successful CHW efforts can be found in programs facilitated by non-governmental organizations or community-based or faith-based organizations.

- Governments can aid CHW programs by placing them within the overall health sector activities, rather than as a separate activity.

This general WHO list of characteristics and expectations is interpreted and modified by country-level and regional health agencies responsible for CHW training. We have seen that the training in many locations has become localized and focused on specific conditions and targeted populations, without broad generalizability to other locations. Further, several training programs are U.S.-specific and do not take into account the burdens often faced by underserved and disenfranchised populations. What may work in the rural United States often is not transferrable to rural Kenya or Nicaragua. In this project, we sought to develop a broad-based CHW training program that would be valid across a wide range of low-resource communities where health systems are most fragile and where physicians and nurses are in dangerously short supply.

The low number of physicians per capita in underserved regions is evidence enough of the need to fill the healthcare gap. At present, in many of these places, the burden of healthcare delivery falls to traditional healers or others with scant knowledge of evidence-based medicine. CHWs offer basic clinical services, yes, but WHO conceives of them as playing a larger role in community health. As we noted above, CHWs are tasked as teachers and accordingly play a critical role in prevention. They are the eyes and ears of medical agencies, bringing information to communities, and through their surveillance functions reporting community health conditions back to the professional healthcare system. A broad-based CHW curriculum must include all these functions.

We want to stress the role of CHWs as bridges, as connectors between communities and outside health agencies. By their presence and their interactions, they convey a message that isolated communities are part of the larger population and that their health problems are visible to agencies outside. Training programs have to recognize that CHWs make a symbolic and practical contribution to establishing a bond between the official health system and outlying communities.

CHW IN-PERSON TRAINING PROGRAM

CURRICULUM DEVELOPMENT

Over two years, WiRED has developed a CHW training program that meets WHO expectations and offers a basic curriculum that is adaptable to any region. Further, it provides a continuing health worker education platform that reinforces the CHW's knowledge base and provides an opportunity to expand skills into new areas of health and community involvement. In this section, we will describe how we developed the program and look at its components.

The process:

We started by compiling a list of topics based on how WHO sees the functions of CHWs, then submitting the draft curriculum to 12 medical professionals (physicians, nursing professors, and health program administrators) in the United States and abroad for comments and suggestions. Was the curriculum list of topics adequate? Did it miss topics important for CHW training? Did the list include unneeded items that would be of little practical use? Where should we focus our course material and how should we apportion the training time in a three-week session? Feedback from the panel guided us in retooling the list with a good sense of where to focus the curriculum. We submitted a second draft and received a final round of comments from the panel. The resulting curriculum was divided into two key blocks:

A core block comprised three training sections:

1. Basic health issues (e.g., anatomy, infectious and non-communicable diseases, healthy practices),

2. Clinical issues (e.g., vital signs and basic assessment, first aid, medication administration),
3. Communications (e.g., basic communications, teaching and health surveillance).

This core block contains topics of relevance to CHWs everywhere. All CHWs must understand anatomy, infectious and noninfectious diseases. They all need to take vital signs, teach health, monitor and report health trends within their assigned communities, and carry out training and surveillance activities. There may be minor differences by location, but on the whole, topics in the core are common everywhere. Where local conditions demand, trainers can adapt material in the core block for local applications.

An elective block allows trainers to select from among more than 400 health topics to localize the curriculum. For instance, malaria, cholera and clean water might be central to much of the work in East African locations. Diabetes, Chikungunya and Dengue would be more relevant to areas in Central America. Trainers can identify the most relevant topics for their CHW trainees. In a test of the CHW program in Kenya described later, trainers recognized the growing relevance of COVID-19, which at the time, was spreading well beyond China. With strong student support, they chose a coronavirus module and a handwashing module as electives.

Why divide the curriculum into a core block and an electives block? We wanted a program that would reflect universal topics for all CHWs and yet would take into consideration local health needs. All CHWs will need to understand basic human health issues. Not all CHWs will likely need to know about frostbite, schistosomiasis or Ross River virus disease. Those who need to understand these conditions/diseases can study them if they wish. The program, thus, unifies all CHW training around a core of universal topics, while affording each region the opportunity to bear down on the health subjects of greatest relevance to that region.

Design of the training modules: The contents of the modules are evidence-based and peer-reviewed; the structure draws from best learning theory, in which narratives develop several key concepts, then brief quizzes reinforce the key concepts. The sequence is repeated: key concepts then related Q&A. Each module presents a comprehensive, computer-scored final exam, a complete list of reference material and an additional resources section comprising PDFs from authoritative sources allowing further in-depth study. Aware that many users will study this material off the Internet grid, we provide PDFs in the additional resources section rather than Internet links which would not be useful.

Distribution of the training material: In distant, low-resource environments, the best developed course material is useless if you cannot get it to users. And so our next challenge was to find a cost-effective, efficient delivery approach for our program — to get the modules anyplace quickly, even to communities residing off the grid.

For years, we distributed our material on CD-ROMs, and as heavy and bulky as they may be, they're a lot better than books and journals, once the only option for training programs. But then shipping CDs became an increasing burden as our library and our audiences grew. Public postal systems in underserved regions are notoriously unusable, and private delivery services (e.g., DHL, FedEx) are too costly and also unreliable. Technology evolved, and we were happy to adopt the more efficient flash drives, a remarkable improvement over CDs; we could pack the contents of a hundred CDs into one drive weighing less than a house key. But still we faced the challenge of getting a parcel from here to there.

Over our 20 years of health training in low-resource communities, we have seen technologies become smaller, lighter, more engaging and interactive, able to reach far more people much more quickly. We looked for a next-generation technology — past the flash drive — that would deliver these modules to distant communities. Thankfully, the Internet evolved in reach and capacity as phone companies and other service providers expanded throughout the world. Offering modules online is an excellent way to make our material available, and, in fact, many people access the modules directly from our server. However, more than half of our target audience is off the grid or has limited Internet access. That may change in time, but for now the challenge was how can we reach them?

The ideal solution would be a web-based application allowing users to download the modules directly to their devices — laptops, tablets and smartphones. The download would be quick, and the stored modules would be sharable — transferring the files offline to other devices, obviating the need for all users to have an Internet connection. The

Internet would be instrumental in distribution — so people could acquire the modules — but not essential for the use of the material. Such an app did not exist, so we turned to a volunteer developer who has worked with WiRED for many years. Within a few weeks, Christopher Spirito came up with a windows and iOS version of the app; several months later he completed an Android version.

What was the outcome? People can now download our modules. Why the excitement? It is difficult to overstate the importance of this electronic link for the CHW training curriculum. Think about a small town or village in Africa, Latin America or Asia. The Internet might be available in a nearby community, but it is slow, not always available, and it is expensive for limited budgets. As these things go, out-of-the-way locations are often in greatest need of health information and trained CHWs.

With the app (we call it Health Module Access Program or HealthMAP), people from a village can go to a nearby town with an Internet connection, and in a few minutes download to their phones or laptops the CHW modules or any other health education material they wish. When they travel back home with the modules, they can work entirely offline. Moreover, they can transfer modules from their device to the devices of friends and colleagues. Those people, in turn, can share the modules with others. A single download, therefore, can ripple throughout a population — and only the first person needs to get online and only for a brief time.

NEXT STEPS: FIELD RESEARCH

Preparations

By mid-2019, we completed the CHW curriculum. It was reviewed and packaged in an interactive format. We had the delivery system ready to go. The next step was to field test the program with trainers and students under the same conditions that would prevail when we rolled out the curriculum. In preparation, we secured the funding and decided on four field test locations that would provide variance in geography, language, economies and social customs. We selected Kenya, India, Nicaragua and Armenia. Our first test site was Kenya.

To set up the Kenya field test, we arranged for two trainers — a clinician and a nurse — with whom we worked via Skype on how to teach the curriculum. We selected 15 CHW students, high school graduates in their twenties with no medical or health backgrounds. Finally, we arranged all the logistics necessary for the three-week course.

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Training

The trainers carefully structured the classes around the CHW curriculum. On a large TV monitor we purchased for the project, trainers went through each module in order and offered supplemental material as necessary to answer student questions and stimulate discussion. Unlike most modules in WiRED's library, the modules in this series are not meant to stand alone, but to structure the flow of material and involve trainers to flesh out details, involve students and localize the content where appropriate. The modules, then, provided content, structure and a forum for interaction.

In addition to participating in classroom instruction, students practiced vital sign measurements (e.g., blood pressure, temperature, heart beat). They also studied a module on teaching techniques and then taught a health topic to others in the group; teaching is a critical function required for CHWs. Students during their process evaluation later told us that the hands-on experience gave them confidence in their skills.

At the end of the course, students took a comprehensive final exam, with items drawn from each module. They also completed a 21-item instrument assessing their attitude toward the course and their views about becoming a CHW including their self-efficacy.

Outcomes

A summary review of the attitude measures is included at the end of this paper. In general, it reports that students agreed that they had acquired the knowledge needed to be a CHW, they were confident that their learned skills will help them succeed as a CHW, and they would recommend the course to friends. Responses varied with respect to the difficulty level and pace of the course. All students said they would be proud to talk about their training with potential employers.

Thirteen of 15 students passed the comprehensive knowledge test with 80% or better. Two missed by a few points. Those two were allowed to study the material for an additional week and retake the exam; both students achieved high passing scores.

Conclusions/recommendations from the Kenya field test:

- The intensive three-week course is appropriate for this training. We were initially concerned about a fatigue factor, but student interest actually grew through the course.
- Engaging a physician and a nurse as trainers was appropriate. Students often showed interest in peripheral issues beyond the training material, and the medical professionals provided appropriate learning.
- Both trainers and students recommended a more comprehensive review of the body's systems. Accordingly, we have rewritten the anatomy section to include a more in-depth study of anatomy and physiology.
- Students requested a rigorous continuing health worker education program. While this follow-up program had already been developed according to WHO requirements, it was good to know students actively sought it, and we didn't have to "sell" the idea.
- Students were eager to download all the CHW modules to their smartphones, and with these programs, they prepared for classes and studied for the final exam. As we described above, they did not need to get online, they had the material on their phones.

NEXT STEPS . . . NOT AS PLANNED

After completion of the Kenya research, we had planned in-person tests of the training program in India, Nicaragua and Armenia, in that order. But like every aspect of life, that plan was abruptly derailed by the coronavirus crisis that has swept the world. The authors of this article, who expected to work with the trainers in India and sit in on the sessions as we had in Kenya, were blocked from traveling out of the United States. Moreover, the instructors and students in India could no longer gather in a classroom.

We were disappointed, of course, but we saw an opportunity and developed procedures to run the entire course online observing these steps:

- We will prepare the trainers via instructional technology platforms. Our original plan called for in-person sessions before classes started, but now all preparation will be online.
- Original plans called for monitoring classroom activities by actually sitting in the class. Now we will monitor the class online as well.
- Trainers will conduct the classes live, but they and the students will be connected via a video link. Students will access the class from tablets, which we will provide.
- We will administer the final exam and attitude measures online.

This all-online approach nudges the project further and faster along than we planned originally, but it also enables us to test a program we will use to fill a pressing need for CHWs that is now made even greater by the coronavirus crisis. Many underserved communities are facing this pandemic without the assistance from medical professionals, where CHWs can have a significant impact on treatment, teaching and surveillance. Moreover, after drugs are developed to address the illness, CHWs will be critical in getting the medications to those who need it and to assisting the vaccination teams who will venture into all communities.

CONCLUSION

We set out to create a training program that would be appropriate in most regions of the world. It would offer the fundamental knowledge and skills required by WHO and seen by medical experts as necessary for CHWs. It would go beyond health services to include the wider range of activities including teaching, prevention and health surveillance. We feel strongly about the CHW's role as a bridge between the official health system and communities, and we stress that in our training.

We met the challenge to distribute the program quickly and easily with an application that allows an individual to download the material one time, then share it freely with any number of others, none of whom need to be on the Internet. As fate would have it, that application has now become ever more important as the coronavirus has forced people to keep a distance, preventing in-person training sessions. We wrote earlier that the best content is useless without adequate distribution. That's especially true now; the tools developed by our volunteers have enabled us to reach the far corners of the earth with valuable health training programs.

As we complete this manuscript, we cannot be certain how the coronavirus crisis will play out, and especially in the underserved regions for which our training program was designed. We are fully aware that health systems are in desperate need of trained people to supplement the professional medical corps. Our first field test demonstrated the success of the program to build the knowledge and skills of CHWs to the point where they would become significant assets in any system reaching out to address growing health needs at this crucial time. The next step, which we could not have envisioned only several months ago, is for us to accelerate the program rapidly to train people who can have a critical impact on a successful outcome of this crisis in communities that otherwise would be underserved, and might go completely overlooked.

AUTHOR DISCLOSURES:

No relevant financial affiliations or conflicts of interest.

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EVALUATION OF COMMUNITY HEALTH WORKER TRAINING KENYA, FEBRUARY 2020

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Participants were asked to complete a 21-item measure upon completion of the CHW course and the course examination. Questions pertained to participants' attitudes toward the course, their intentions to become a CHW, selective norms, and their perceived behavioral control. Analyses were completed on each of the measures, first to determine the extent to which the items within a construct (e.g., Attitude, Intention) hung together. The coefficient of internal consistency for each of the scales was: .62, .68, .76, and .72, respectively, which are good given the rather short scales and the small sample. This suggests that the items within each of the scales were tapping a similar construct.

In addition, we ran a t-test on each item, contrasting the obtained score with the midpoint (neutral) scale rating (which was 3). In every case, the obtained item rating, across all 21 items, differed significantly (at $p < .001$) from 3. This means the students' attitudes toward the course were significantly more positive than neutral, that their intentions were positive, and significantly different from neutral, their intentions to become a CHW were more positive, as were their perceptions of behavioral control (i.e., they felt empowered to become a CHW).

Eighty percent of the participants strongly agreed that after the course, they had the knowledge needed to be a CHW, with the remaining 20% agreeing. Seventy-five percent strongly agreed that they would succeed in their goal to become a CHW, with the remaining 25% agreeing. Ninety-three percent were confident that their skills after this training would help them succeed as a CHW, with the remaining 5% agreeing.

Around 90% of the participants strongly agreed that the course content was interesting, that the course materials provided valuable information, that the course provides a strong foundation for a career as a CHW, and that they will recommend this course to their friends who are interested in becoming a CHW. The remaining participants agreed. All but two participants either strongly agreed or agreed that the course exceeded their expectations. Responses varied as to the difficulty level of the course and the pace of the course, which is to be expected given the different backgrounds of the participants, with 73% strongly agreeing or agreeing that the difficulty level was appropriate and 80% strongly agreeing or agreeing that the pace was appropriate. Two of the 15 responses to the pace question were neutral about the pace.

All participants either strongly agreed (87%) or agreed that they intend to become a CHW and that the course materials were relevant to their training as a CHW, with 73% strongly agreeing. Eighty percent strongly agreed that they intend to seek more training in community health, with the remaining agreeing. Two-thirds strongly agreed that becoming a CHW would help them achieve an important personal goal, with the remainder agreeing, except for one who was neutral.

All participants strongly agreed (86%) or agreed that they will be proud to talk about their CHW training to potential employers, that their family would be proud if they became a certified CHW (80% strongly agree) and that becoming a CHW would bring honor to their significant others (e.g., family, friends) (80% strongly agree). Nearly all students stated that they agree (agree or strongly agree) that their friends would be happy for them to be a CHW and that the community would be happy if they became a CHW. All but one participant strongly agreed that becoming a CHW would be a great benefit to their community, though only 53% stated that they strongly agreed that their community would welcome them as a CHW, with all but one (who was neutral) stated that they agreed.

Polycythemia

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ABSTRACT

Polycythemia is a disease state in which the red blood cell numbers are increased in the blood (erythrocytosis), which in turn makes blood thicker and can cause circulatory problems. Polycythemia Vera is a stem cell disease belonged to a group of myeloproliferative neoplasm in which the erythroid progenitors are overly proliferated by acquired mutation of the JAK2 gene, resulting in excessive erythrocytosis. Secondary Polycythemia refers erythrocytosis due to underlying conditions. It is usually associated with increased blood erythropoietin levels as a compensatory reaction to tissue hypoxia, which can be seen in patients with chronic lung disease or sleep apnea or living at high altitudes. Certain tumors produce the erythropoietin and testosterone increases the blood erythropoietin level, resulting in secondary polycythemia. Relative polycythemia is the consequence of plasma volume contraction, falsely raising the RBC count and hemoglobin/hematocrit level in CBC. Two cases of polycythemia are presented: 1) a patient with polycythemia vera and 2) a patient with secondary polycythemia. Various types of polycythemia are discussed with an updated review covering the etiology, clinical manifestation, diagnostic approach and treatment.

INTRODUCTION

Polycythemia refers to an increase in erythrocytes (red blood cells: RBCs) in the body. Too many RBCs cause the blood to be thicker, which in turn, increases the risk of various health problems. Polycythemia can have different causes, and each of them has its own treatment options.

The principal function of erythrocyte is the transport of oxygen. Erythropoiesis proceeds at a rate consistent with the demand for oxygen-carrying capacity, and the major regulator of erythrocyte production is erythropoietin (EPO). EPO is produced primarily by the kidney under control of a tissue oxygenation sensor.[1]

Secondary erythrocytosis results from either physiologically appropriate compensation for inadequate tissue oxygenation which can be seen in patients with lung disease or from inappropriate stimulation of erythropoiesis by EPO-producing tumors or by testosterone therapy. Erythrocytosis increases oxygen-carrying capacity of the blood, but at high hematocrit levels increased blood viscosity may result in decreased tissue oxygen delivery.[2,5]

However, if the bone marrow keeps producing RBCs without any reason, it is called Primary Polycythemia or

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Polycythemia Vera (PV). The PV is a trilineage, Philadelphia chromosome–negative myeloproliferative neoplasm (MPN) characterized by chronic, unregulated proliferation of erythrocytes and leukocytes and/or platelets.[2] Although leukocytosis and thrombocytosis frequently accompany, erythrocytosis is the most prominent clinical expression of PV.[2,3] A somatic (non-hereditary) mutation (V617F) in the JAK2 gene is found in almost all cases of PV.[3]

Relative polycythemia is an apparent rise of the erythrocyte level in the blood; however, the underlying cause is reduced blood plasma. Relative polycythemia is often caused by loss of body fluids, such as through burns, dehydration, and stress.[3]

CASE REPORT 1

A 76-year-old Hispanic woman was referred for a hematology consultation with increased hemoglobin and platelet counts. CBC showed:

- WBC 7.9 k/uL
- RBC 6.45 mil/uL
- hemoglobin 16.3 k/uL
- hematocrit 51.5%
- MCV 79.3
- platelet 512 k/uL

She has occasional headaches and mild generalized weakness which she attributes to her old age. She denied chronic cough, dyspnea, chest pain, dizziness, excessive snoring, or pruritus. She has no significant medical history such as lung disease, cancer, stroke or coronary artery disease and her only medication is aspirin 81 mg/day. She doesn't use tobacco or alcohol. The family history is not contributory. The comprehensive metabolic panel was not remarkable. Physical examination showed BP 110/70, pulse oximetry in room air 97%, regular pulse at 63/min, no peripheral lymphadenopathy, clear lung sound and normal heart sound, no hepatosplenomegaly, trace leg edema, and varicose veins in lower legs. She had a red face. The EPO level was abnormally low at 1.6 mIU/mL (normal; 2.6-18.5). Because PV was strongly suspected, JAK2 V617F mutation was ordered, which came back positive. The serum ferritin level was lower-normal at 34 ng/mL. She was diagnosed to have PV, and hydroxyurea was started at 500 mg a day. The hemoglobin, hematocrit and platelet counts were gradually decreased. She felt much more alert and energetic, which were noticed by her daughter. The CBC done 3 months later showed:

- WBC 7.1 k/uL
- hemoglobin 14.3 g/dL
- hematocrit 41.5%
- platelet 391 k/uL

CASE REPORT 2

A 65-year-old white man was referred for a hematology evaluation because of increased hemoglobin and hematocrit at 18.5 g/dL and 54.2 % respectively. The RBC count was 6.17 mil/uL (normal 4.2-5.80), WBC 5.5 k/uL and platelet 243 k/uL. He had no history of chronic lung or heart disease. He was not a smoker. He was taking metoprolol and losartan for hypertension. Because of hypotestosteronemia causing low energy level and libido, he was on testosterone implant therapy.

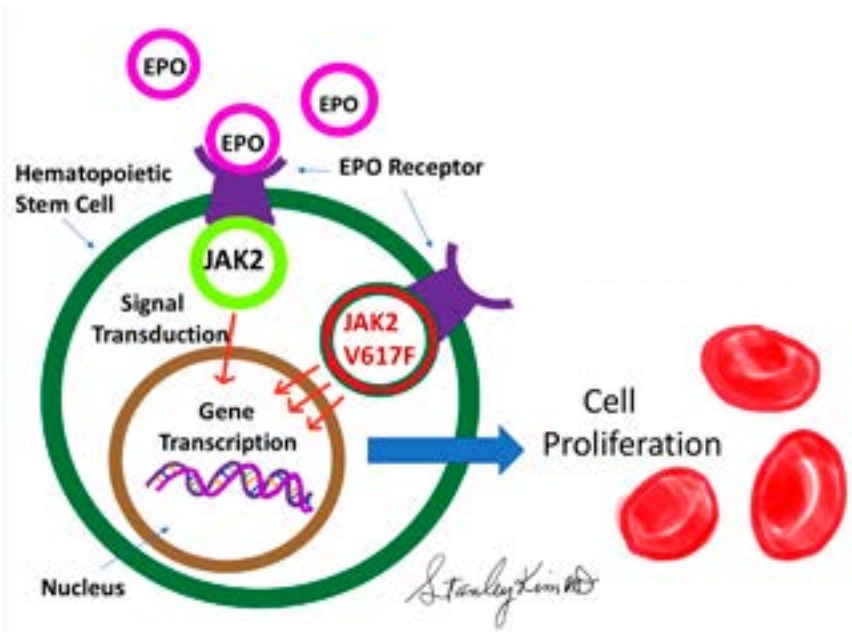
Physical examination showed BP 140/62, pulse oximetry in room air 97%, noticeably red face, no peripheral lymph node enlargement, normal heart and lung sounds, and no hepatosplenomegaly. The serum testosterone level was measured and was within normal limit at 654 ng/dL (normal; 250-827). The serum EPO level was also normal at 7.1 mIU/mL. Before investigating further for polycythemia, he was advised to stop the testosterone therapy and repeat CBC. The testosterone level decreased to 354 ng/dL as did the hemoglobin/hematocrit to 15.5 g/dL and 45%.

DISCUSSION

Clinicians may encounter polycythemia in the course of evaluating other clinical findings or incidentally on a routine laboratory test with complete blood count (CBC). The initial evaluation should enable the clinician to distinguish between relative polycythemia by plasma volume depletion from absolute polycythemia. Findings from the initial evaluation, together with the clinical scenario, should direct the subsequent evaluation to establish the underlying diagnosis.

FIGURE 1.

Normally, **JAK2** regulates erythropoiesis in response to the EPO. In Polycythemia Vera, the mutated **JAK2 V617F** can activate the signal transduction without EPO resulting in excessive erythropoiesis.



CAUSES AND CLINICAL MANIFESTATIONS OF POLYCYTHEMIA

Polycythemia Vera

Polycythemia Vera (PV) is a part of the myeloproliferative neoplasm (MPN). Other hematological conditions belonged to MPN include primary myelofibrosis, essential thrombocythemia and chronic myeloid leukemia.[2] It is caused by a mutation in a gene (JAK2) resulting in uncontrolled production of erythrocytes by the bone marrow. Normally, JAK2 regulates erythrocyte and platelet production in response to the EPO or TPO (thrombopoietin). But the mutated JAK2 (most commonly JAK2 V617F mutation) activates the signal transduction of hematopoietic stem cells in the absence of EPO or TPO. (Fig 1.). As a result, excessive erythrocytosis or thrombocytosis occurs without EPO or TPO stimulation.[2,3]

A somatic mutation (V617F) in the JAK2 gene is found in almost all PV patients. A study reported that 97% of PV patients are positive for the exon 14 V617F mutation, and the remaining 3% are positive for exon 12 V617F mutation, suggesting that either an exon 14 or 12 JAK2 mutation is present in virtually all patients with PV.[2,3] The JAK2 mutation is absent in normal subjects as well as those with secondary polycythemia. Thus, this mutation, when present, enables one to distinguish patients with PV from those with secondary polycythemia. However, the finding of the JAK2 V617F mutation is not specific for PV, since it is also present in a substantial proportion of patients with essential thrombocythemia (ET) as well as primary myelofibrosis.[6]

Symptoms of PV include headache, dizziness, generalized weakness, tinnitus, visual disturbances, chest pain, poor circulation of extremities, red face, and erythromelalgia. One of the interesting symptoms of PV is itching after warm bath occurring in 40% of patients due to high blood histamine level. The Histamine increases stomach acid secretion, which can cause peptic ulcer disease and stomach bleeding resulting in iron deficiency anemia. Splenomegaly is seen in 75% of patients and hepatomegaly in 30%.[7] Increased level of circulating RBCs increases the viscosity of the blood. This can be associated with high risk of thrombosis leading to stoke, acute coronary disease, deep vein thrombosis of extremities and pulmonary embolism.[8] High turnover rate of the blood cells results in high uric acid production, which can cause gout and uric acid kidney stones.[7]

Transformation to myelofibrosis (MF) and/or acute myeloid leukemia (AML) is a significant cause of mortality in PV and is likely largely related to disease duration. In large studies, progression to MF was reported in 9% to 21% of patients with PV, while evolution to AML has been documented in 3% to 10% of patients with PV. Risk factors for transformation include older age and leukocytosis.[9]

Secondary Polycythemia

When the body feels lack of O2 (hypoxia), the kidney produces erythropoietin (EPO) which is a hormone that promotes formation of RBCs by the bone marrow.[1] Conditions causing tissue hypoxia include chronic lung diseases (COPD), sleep apnea, cyanotic heart disease with right-to-left shunt, and living at high altitude. When tested with an oximetry, patients often have low O2 saturation.[5] However, secondary polycythemia due to chronic carbon monoxide poisoning do not show abnormally low O2 in the oximetry test. Chronic carbon monoxide poisoning is caused by heavy smoking, or malfunctioning gas heater or chimney.[10]

Certain tumors can produce the EPO, causing polycythemia: hepatocellular carcinoma, uterine fibroid tumor (leiomyoma), renal cell carcinoma, hemangioblastoma of the brain, meningioma, and pheochromocytoma.[11] Therefore, investigation for the underlying neoplasm should be considered when no other causes of secondary polycythemia are found. Increased EPO production can be the cause of secondary polycythemia after kidney transplantation or renal artery stenosis. The exact cause of polycythemia in those kidney problems is not known but appears to be related with decreased perfusion to the kidney. Testosterone increases the EPO level and decreases Hepcidin level, which result in erythrocytosis.[11]

Relative Polycythemia

Relative polycythemia is caused by decreased plasma volume and is often caused by loss of body fluids, such as through burns, dehydration, and stress.[2] Gaisbock's syndrome is an interesting relative polycythemia having a constellation of signs and symptoms: mild obesity; elevation of blood pressure (especially diastolic); decrease in plasma volume with relative increase in red cell count, hemoglobin, hematocrit, viscosity of blood, elevation of plasma proteins, serum cholesterol, triglycerides, uric acid, and plasma renin; and increased excretion of urinary sodium.[4]

Congenital Polycythemia

Primary familial and congenital polycythemia (PFCP) is a rare disease characterized by isolated erythrocytosis in an individual with a normal-sized spleen and absence of disorders causing secondary erythrocytosis. Patients have normal hemoglobin oxygen affinity measured as P50. The EPO level is low or in the lower normal range. It is inherited by autosomal dominant pattern.[7]

Altered oxygen affinity variant hemoglobins (Hb) are caused by mutations of the globin genes. Changes in Hb oxygen affinity shift the oxygen dissociation curve, which can be identified by abnormal P50 measurements of patient RBCs. Variants are categorized as either low oxygen affinity (high P50) or high oxygen affinity (low P50).[8]

DIAGNOSTIC APPROACH

Diagnostic approach of polycythemia starts at a through history and physical examination to determine the likely causes of high hemoglobin/hematocrit. Various symptoms and signs of primary and secondary polycythemia should kept in mind, including pulmonary symptoms, sleep apnea, smoking, itching after warm bath, dehydration, use of testosterone, the size of spleen, living at high altitudes, pulse oximetry result, etc. Measurement of the serum EPO level can distinguish secondary from primary polycythemia: if it is normal or high, secondary polycythemia is suspected, and if it is low, primary polycythemia (polycythemia vera). However, when patients with PV have underlying condition causing hypoxia such as COPD, the EPO level may not be low. The JAK2 mutation test is important. As the JAK2 mutation in exon 14 or exon 12 is seen in almost all patients of PV, it is difficult to diagnose PV without its positivity. The 2016 WHO criteria for the diagnosis of PV include the following:

Major criteria:

1. Increased hemoglobin level (>16.5 g/dL in men or >16.0 g/dL in women), hematocrit (>49 percent in men or >48 percent in women), or other evidence of increased red cell volume;
2. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size);
3. JAK2 V617F or JAK2 exon 12 mutation.

Minor criterion: Serum erythropoietin (EPO) level below the reference range for normal.

The diagnosis of PV requires the presence of all three major criteria or the presence of the first two major criteria

together with the minor criterion. These diagnostic criteria should be applied only to patients who have undergone the appropriate diagnostic evaluation to exclude secondary causes of polycythemia. The second major criterion (bone marrow biopsy) may not be required in cases with sustained absolute erythrocytosis (hemoglobin >18.5 g/dL or hematocrit >55.5 percent in men; hemoglobin >16.5 g/dL or hematocrit >49.5 percent in women) if the third major criterion and the minor criterion are present. Although, bone marrow biopsy may not be necessary to make a diagnosis of PV in certain cases, it is helpful to distinguish PV from other MPN such as essential thrombocythemia or myelofibrosis.[12]

Congenital polycythemia can be considered when polycythemia occurs in young children especially with a family history of polycythemia.

TREATMENT OF POLYCYTHEMIA

Polycythemia Vera

Low risk patients (younger age < 60 years; no history of venous or arterial thrombosis) just need therapeutic phlebotomy to keep Hct < 45%. All others are considered high risk and require cytoreductive therapy with phlebotomy as needed. Because the main goal of therapeutic phlebotomy is to induce iron deficiency to keep the hematocrit under the 45%, iron therapy is not recommended. However, in our experience of 30 years of medical practice, we have observed that patients with iron deficiency often complain of symptoms such as generalized weakness, headache, dizziness, difficulty in concentration, or restless leg syndrome. In those patients, cytoreductive therapy is preferred to reach the goal rather than inducing severe iron deficiency by multiple therapeutic phlebotomies. Practically, we prefer hydroxyurea for most patients with PV because of its quick onset of action and low risk of leukemogenesis,[9,13] but pegylated Interferon (IFN) alfa is the choice for younger patients (eg, <40 years) and those who might become pregnant.[14]

All patients need low dose aspirin unless the platelets > 1 mil/uL. Acquired von Willebrand Disease can develop in patients with PV, especially when the concomitant platelet count is very high,[15] in which case aspirin is contraindicated due to high risk of bleeding.

Severe pruritus and erythromelalgia are usually respond to low dose aspirin. For refractory pruritus, severe splenomegaly or post-PV myelofibrosis, ruxolitinib (JAKAFI®: JAK Inhibitor) is indicated. Alkylating agents such as Busulfan and radioactive phosphorus (^{32}P) have been used for elderly patients, but it can increase the incidence of acute leukemia.[13]

Anagrelide (Agrylin) is not preferred as a first line Tx because of high incidence of arterial thrombosis, major bleeding and myelofibrosis side-effects.[14]

Secondary Polycythemia

The management of secondary polycythemia should be focused on the treatment of underlying causes. Because secondary polycythemia is compensatory phenomenon to the hypoxic environment, patients may benefit from increased erythrocytosis. However, at certain point, too may RBCs result in increased blood viscosity, impairing tissue perfusion. Therefore, when patients develop symptoms of severe polycythemia, careful phlebotomy can relieve the symptoms and make patients feel better. In my practice, I phlebotomize patients with secondary polycythemia when the hemoglobin is above 20 g/dL, especially patients don't feel well with headache or generalized weakness.

AUTHOR DISCLOSURES:

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The Potential of Andexanet Alfa as a Reversal Agent for Direct Oral Anticoagulants

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Andexanet Alfa, Bleeding Complications, Direct Oral Anticoagulants, Reversal Agent

ABSTRACT

Purpose: The purpose of this article is to describe the role of andexanet alfa as a reversal agent in the management of bleeding complications associated with direct oral anticoagulants (DOACs).

Summary: Over the past several years, DOACs are increasingly being used in the management of patients with non-valvular atrial fibrillation or stroke prevention. Management of major bleeding in DOAC therapy includes supportive therapy and addressing any factors that are contributing to blood loss. Additionally, there may a need to expedite the removal of any anticoagulation effects by removing or neutralizing the anticoagulant. Until recently, there was no specific reversal agent for DOACs; management approaches were limited to utilizing concentrated clotting factors or fresh frozen plasma. The FDA granted expedited approval of andexanet alfa as a specific reversal agent for the DOACs to meet this unmet need.

Conclusion: In clinical trials, andexanet alfa demonstrated a significant reduction in anti-Xa activity in patients with a major bleeding event on apixaban or rivaroxaban. The clinical benefit of this anti-Xa activity reduction has yet to be demonstrated in a randomized controlled trial. The current lack of randomized controlled trials demonstrating clinical benefit and the high cost of the drug has limited the widespread use of this antidote.

INTRODUCTION

Major bleeds associated with factor Xa (FXa) inhibitors contribute to high dollars and long lengths of hospital stays. The most common bleeds associated with FXa inhibitors are intracranial, gastrointestinal, and bleeds occurring in critical sites that may be associated with hemodynamic instability.

Management of hemorrhagic complications associated with FXa inhibitors is primarily supportive care. If a bleed is not associated with hemodynamic instability and is not life-threatening, then the recommended management is to discontinue the offending agent and initiate mechanical compression, surgical intervention, fluid replacement, and hemodynamic support, and/or blood product transfusion. However, if the bleed is emergent and life-threatening (i.e., signs or symptoms of hemodynamic compromise, acute overt bleeding associated with a decrease in hemoglobin level of greater than two, or acute symptomatic bleeding in a critical area or organ) then in addition to general measures, initiation of a reversal agent should be considered. As there are limited options for FXa inhibitor reversal, Four Factor Prothrombin concentrate complex

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(4F-PCC, KCentra, which is approved for urgent reversal of Vitamin K antagonists such as warfarin. The use of 4F-PCC for FXa inhibitor reversal is off-label and theoretically works by overwhelming the anticoagulant effects of FXa inhibitors in a non-specific manner. The lack of specificity of 4F-PCCs' anticoagulant effects can result in an increase potential to produce thrombin. 4F-PCC does not affect anti-Xa levels. Despite sparse clinical data from patients with bleeding complications, clinical reports and studies have suggested that 4F-PCC does have a potential role in the management of DOAC-associated bleeding. However, there are no clinical studies directly comparing 4F-PCC with specific antidotes and limited data are available regarding the incidence of thrombosis in patients receiving reversal with 4F-PCC, which led researchers to search for a more specific reversal agent for FXa inhibitors.[1, 2]

Due to an unmet medical need for patients treated with direct FXa inhibitors when reversal of anticoagulation is needed, in May 2018, AndexXa is also known as andexanet alfa (Portola Pharmaceuticals, Inc.)[3] earned accelerated approval from the Food and Drug Administration (FDA) as a specific reversal agent for apixaban- and rivaroxaban-treated patients with life-threatening or uncontrolled active bleeding.[4] Andexanet alfa is a modified recombinant form of FXa which has a high binding affinity to FXa inhibitors (apixaban and rivaroxaban) and sequesters them, thus allowing native FXa to restore thrombin generation used for clot formation. Furthermore, it has an off-target pro-thrombotic effect by binding and blocking the tissue factor pathway inhibitor (TFPI), which is a key regulator in preventing excessive clotting.[5] Pharmacokinetic (PK) and pharmacodynamic (PD) studies have shown that andexanet alfa has a rapid onset and a PD half-life of one hour.

The combined ANNEXA clinical trial assessed the percent reversal of anticoagulant effect by measuring the anti-FXa level in the plasma of healthy volunteers after reaching a steady-state on apixaban or rivaroxaban. The study concluded that there was a 92% reduction in anti-FXa activity in patients on apixaban and a 97% reduction in anti-FXa activity in patients on rivaroxaban. Andexanet alfa also successfully reduced anti-FXa activity within two to five minutes after the bolus dose. The addition of a continuous infusion increased the duration of these effects for an additional two hours after completion of the infusion. This concluded that the administration of andexanet alfa resulted in a rapid elevation of thrombin generation following the bolus dose. Nevertheless, the study was limited by populations that had few risk factors for signs and symptoms of bleeding. Moreover, no major reports of serious, severe adverse reactions or thrombotic events were reported.[7] Thus, it is uncertain whether andexanet alfa would improve outcomes in patients with major bleeds.

ANNEXA-4 was a prospective, open-label study in which patients with FXa inhibitor-associated acute major bleeding received andexanet alfa as an antidote. The study determined that administration of andexanet alfa rapidly and substantially reversed anti-FXa activity when administered as a bolus and sustained this reversal when followed by an infusion. Overall, about 82 percent of patients achieved excellent or good hemostasis over 12-hours following infusion. Achievement of excellent to good hemostatic efficacy for intracranial hemorrhage (ICH) or gastrointestinal (GI) bleed was defined as an increase in hematoma volume or thickness of greater than 20 percent but less than 35 percent compared to baseline or less than 20 percent decrease from baseline hemoglobin and hematocrit. The study coordinators hypothesize that a reduction in anti-FXa activity was a predictor of clinical response. However, when plotted on the receiver operator characteristic (ROC) curve to measure the sensitivity and specificity of the test, it indicated that there was no significant relationship between hemostatic efficacy and reduction of anti-factor Xa activity after treatment. During the 30-day follow-up period, thrombotic events occurred in 10 percent of patients and death occurred in 14 percent of patients. The events occurred within the range expected in this population, given the severity of the bleed, underlying thrombotic risk, and time to restart anticoagulant therapy following their episode. The study included many limitations such as a notable exclusion that omitted patients who had planned surgery within 12 hours, ICH with Gasglow score (GCS) of less than seven and a hematoma volume greater than 60 milliliters, suffered from a thrombotic event within the last 14 days or received previous treatment with PCC, recombinant FVIIa, or blood. The population omitted represents a large gap where the administration of andexanet alfa may be most beneficial.

Moreover, baseline characteristics were consistent as the mean patient age was 77, white, males, on FXa inhibitor for atrial fibrillation (A.fib). Most of the bleeds were ICH (64 percent) with a median GCS of 14 and GI bleed (26 percent).[8]

The FDA Accelerated Approval Program (AAP) based its approval of andexanat alfa on surrogate endpoints rather than clinical outcomes. The AAP will require the manufacturer to perform Phase 4 trials to confirm clinical benefit. Although there are currently no head to head trials comparing 4F-PCC and andexanet alfa, based on the data from these clinical trials, the American College of Cardiology (ACC) Guidance for Anticoagulation Reversal, 2019 American Heart Association Task Force, Heart Rhythm Society, and ACC Guideline Update for Management of Patients with A.Fib, and CHEST Guideline and Expert Panel Report all support the use of a andexanet alfa for patients presenting with severe or life-threatening bleed caused by apixaban and rivaroxaban superseding the off-label use of 4F-PCC.[10-12]

Before the administration of andexanet alfa, it is important to assess the patient for the recent use of apixaban or rivaroxaban. During the initial evaluation, providers must assess vital signs, physical examination, source of the bleed, and patients' eligibility for reversal.[6] If andexanet alfa is warranted, the drug must be administered in two parts: bolus followed by an infusion. Andexanet alfa has two dosing regimen: standard and high dose. The standard-dose regimen consists of a 400 mg intravenous (IV) bolus given at a rate of 30 milligrams per minute, followed by a two-hour IV infusion given at a rate of 4 milligrams per minute. The high dose is an 800 mg IV bolus given at a rate of 30 milligrams per minute, followed by a two-hour IV infusion given at a rate of 8 milligrams per minute. The recommended regimen for a patient is based on the FXa inhibitor used, the dose of FXa inhibitor, and the time since the last dose of FXa inhibitor. The recommendations are summarized in Table 1. Since andexanet alfa has a quick onset and a half-life of one hour, it is encouraged to start the infusion without delay after the bolus dose. Therapeutic monitoring includes signs and symptoms of clinically relevant bleeding and thromboembolic events.[7]

There are no recommendations for dosage adjustment in patients with renal or hepatic dysfunction. Some adverse reactions include antibody development (6-17%), infusion related reaction (18%), deep venous thrombosis (DVT), ischemic stroke, acute myocardial infarction (MI), pulmonary embolism (PE), cardiogenic shock, cardiac failure, urinary tract infection (UTI), pneumonia, and acute respiratory failure. Contraindications include hypersensitivity to the andexanet alfa or to its inactive ingredients. The FDA issued a box warning and precautions for the risk for a thromboembolic event, ischemic risk, cardiac arrest, and sudden death.[7] Due to the possibility of serious adverse effects, patients must be continuously monitored during and after administration.

TABLE 1.
Summary of Recommended Regimens

DRUG FXa Inhibitor	DOSE Strength of Last Dose	TIME Since Last Dose Taken	
		< 8 HOURS OR UNKNOWN	≥ 8 HOURS
APIXABAN	≤ 5 mg	Standard dose	Standard dose
	> 5 mg or Unknown	High dose	
RIVAROXABAN	≤ 10 mg	Standard dose	Standard dose
	> 10 mg or Unknown	High dose	

To decrease the risk of thrombotic events and deaths, it is important to restart the patient's oral anticoagulant (OAC) once stable and when the clinical indication for continued anticoagulation is clear. If the patient had a bleed in a critical site or is at high risk of rebleeding, death or disability, or source of bleed has yet to be identified, then the patient may not be a candidate to be restarted on OAC. A majority of thrombotic events and deaths occurred in patients whose resumption of OAC was delayed or in patients who did not restart anticoagulation. In the clinical study, patients who were resumed on did not have any thrombotic events during the 30-day follow up.[8] This emphasized the importance of placing prothrombotic patients back on an anticoagulant if probable and as soon as possible. However, the timeframe after administration to restart anticoagulation is still uncertain and the data suggests restarting between 5 to 30 days after treatment.

Cost considerations have become a barrier to its addition to hospital formularies. The average cost of a 200 mg vial of andexanet alfa is around $6,600. The standard dose treatment would require a total of five 200 mg vials, which would cost approximately $30,000. The high dose treatment would require a total of nine 200 mg vials, which would cost

approximately $59,400.[13] In comparison, treatment with 4F-PCC for a typical patient based on 50 units/kg dose would be approximately $14,500.

Several unanswered questions still linger with the use of andexanet alfa. Is andexanet alfa more effective than the standard of care? If a patient requires emergent surgery or procedure, can andexanet alfa use? If a patient continues to bleed despite administration, is a second dose safe? How will andexanet alfa be measured in serum for the cessation of bleeds? Upcoming clinical trials with anticipated completion by Portola Pharmaceuticals Inc. is expected to evaluate the efficacy and safety of andexanet alfa versus standard of care in patients with ICH anticoagulated with a direct oral anticoagulant (DOAC).[9]

CONCLUSION

Andexanet alfa is the first FDA-approved agent for the reversal of anticoagulation in patients treated with apixaban or rivaroxaban. It is not approved to reverse the effects of other factor Xa inhibitors. This agent can markedly decrease the anti-FXa activity in the serum within two minutes of administration. Despite its relatively high cost, andexanet alfa does demonstrate favorable potential in managing life-threatening bleeds for patients taking either apixaban or rivaroxaban in an uncontrolled study. However, to support standardized use in critical care practice, more evidence-based data from a controlled study directly comparing andexanet alpha with prothrombin concentrate complex is necessary.

AUTHOR DISCLOSURES:

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Visual Conversation Tools: Helping Patients to Make Better Medical Decisions

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KEYWORDS:

Outcome Roadmap, Patient-Doctor Communication, Risk-Benefit analysis

ABSTRACT

Clinicians are often told to use simple language to help patients understand, but that is easier said than done. Not only are you supposed to communicate in easy-to-understand language, but you are also supposed to communicate complex information as simply as possible. The other complicating factor is that people learn best by using multiple modalities such as Gardner's seven styles of learning: visual, physical, aural, verbal, logical, social, and solitary.[1] But what do we do all day? We talk and talk and talk. And the patients aren't listening. My goal is to show you how to communicate more visually and experientially. As a bioethicist with specialized training in mediating conflicts, I know that when people have better and more relevant information, they make better decisions. I am going to demonstrate the visual tools you can use to improve informed consent and complex decision making. These tools are designed to help patients learn how to make sense of the overwhelming and complicated information they are receiving.

DRAWING AN OUTCOME ROADMAP

As a family caregiver for six members of my family, I have sat through a lot of informed consent conversations. I have seen clinicians focus on good outcomes while glossing over the adverse outcomes. And research shows that patients do the same thing. "The majority of participants overestimated intervention benefit and underestimated harm. Clinicians should discuss accurate and balanced information about intervention benefits and harms with patients, providing the opportunity to develop realistic expectations and make informed decisions."[2]

This increases the amount of hope and wishful thinking in making medical decisions. For many patients, the best outcome is definitely a possibility. But for others, even with the best care, bad things can happen, and certain treatment paths may become inaccessible. When this happens, patients need to be willing to change course and choose from the paths that are still available to them. To help visualize the treatment roads which are truly available for the patient, it is helpful to draw an Outcome Roadmap.[3]

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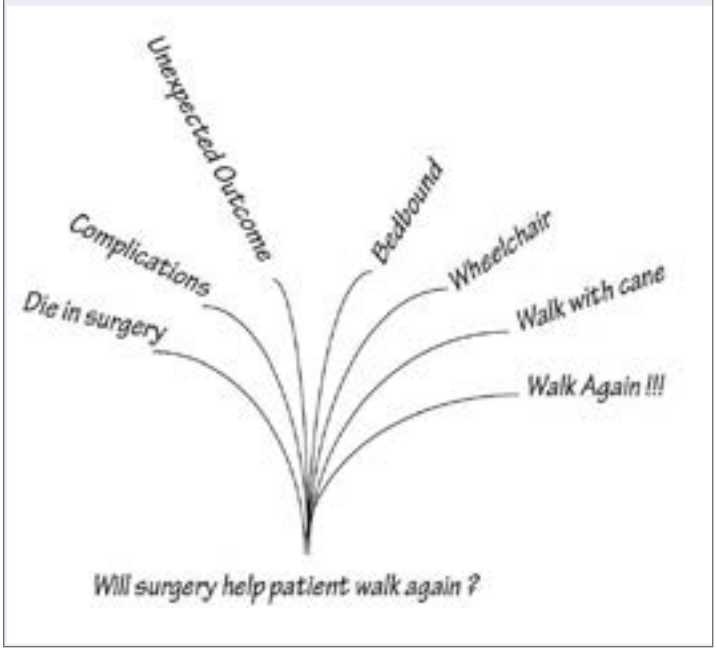
FIGURE 1.
Outcome Roadmap



INSTRUCTIONS FOR DRAWING OUTCOME ROADMAP

Step 1: Prepare for the conversation. Before you walk in to discuss surgery for a person who has been in a car accident, sketch out some possible outcomes that you want to discuss.

Step 2: Bring a blank piece of paper in with you because you will be sketching out the outcomes with the patient in real-time. Do not do all the talking. Instead, ask the patient what she hopes will happen after the surgery as well as what she would consider a bad outcome.

Step 3: Put a large dot on the bottom of the page and say, "Here is where you are today." Then begin by drawing the positive outcomes to the right. I usually start with what I know people want. "I know you would like to be back to normal." Even if this isn't possible, I still draw the "normal" road because in a few minutes, I will use this as an opportunity to manage her expectations as I explain that unfortunately, that road is closed.

Step 4: If she tells me she is hoping for a certain outcome that I know is not possible, I will still draw it. Then gently and compassionately, I will cross off the road demonstrating that some outcomes are not available even though they are desired. You can draw this by putting your pen on the starting dot and then move your pen along the desired road. Partway down the road, put an x on the road and slide your pen back down to the starting point. Explain to her that she will have to travel a different road. Then discuss and draw the roads that are still available for her.

Step 5: On the far left, draw the negative outcomes that you hope won't happen. Taking the time to draw these other paths allows her to "see" what you are saying and to discuss her fears and concerns.

Step 6: In the middle, draw the possible neutral, unexpected or unknown outcomes. You can label these as "unknown outcomes" and "unexpected complications." This will help her to understand that you can't promise her a guaranteed result.

Step 7: As you explore different options, explain that you will work toward the best outcomes but sometimes, a road becomes blocked and you may have to turn around and take a detour.

Step 8: Over time, you can add or delete roads based on how her condition progresses.

DISCUSSING THE RISKS, BENEFITS AND BURDENS

As professionals, we are used to discussing the risks, benefits and alternatives. What is often missing in our conversations is a discussion of the burdens. Here is how I explain these categories in language patients can understand.[4]

Risks: The bad things that might happen if you choose the treatment/no treatment.

Benefits: The good things that might happen if you choose the treatment/no treatment.

Burdens: What it will feel like and be like for the patient to experience the treatment/no treatment choice. This may include pain, suffering, side effects, disability, effort, time spent, financial costs, etc.

For each decision, the patient, or decision maker using the patient's values, gets to decide if the treatment being offered would provide a worthwhile outcome and if she would be willing to endure the potential risks and burdens. To address this I will discuss, "What will the treatment do for the patient? And what will the treatment do to the patient?"

FIGURE 2.
Weighing the Options - Risks, Benefits and Burdens

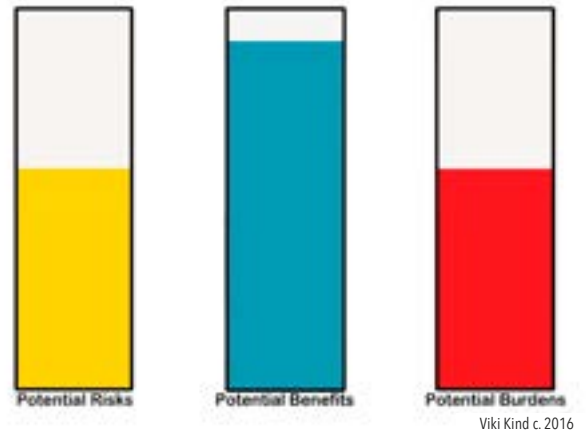
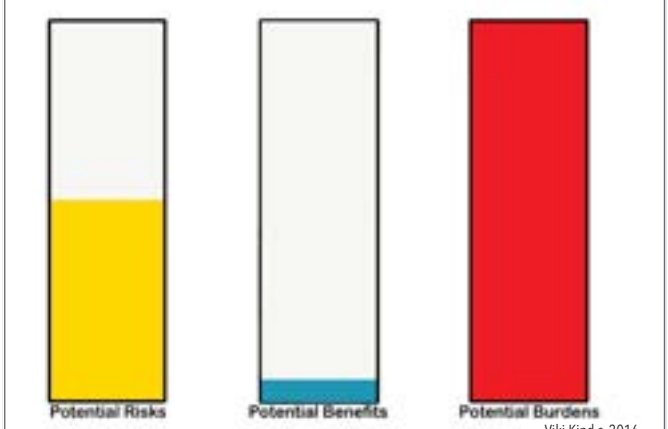


FIGURE 3.
Weighing the Options - Risks, Benefits and Burdens



I will also talk about how the consequences will play out in the long term by answering the question, "And then what?" This question reminds both us and the patient that the consequences are not just what happens inside the hospital, but what will happen out into the person's daily life. And as professionals and family members, we must accept that what the patient decides is worthwhile may be different from what we think would be worth the risk. We respect the patient's wishes because it is the patient who will have to live with the burdens of the decision long term.

WEIGHING THE OPTIONS CONVERSATION TOOL

We use the weighing the options tool to help the patient visually document their perceptions of and opinions about the treatment choice.[3] The family and/or healthcare professional can also draw their views of the treatment experience to see how their perceptions may be different from the patients.

Ms. B has ESRD and needs dialysis. Does Ms. B think dialysis will benefit her and does she understand the risks and burdens? You can have her draw what she "thinks" it will be like to both receive dialysis and to live with the consequences of dialysis. Because you can see how she imagines it, you will have the opportunity to clarify any misperceptions. (If you don't know what it is like to receive and live with the consequences of dialysis, you can talk to or read about other patients who have gone through this experience. There are many personal blogs that describe what if feels like to experience and live with different treatments and diseases.) Once Mrs. B is actually receiving dialysis, you will want her to complete the Weighing the Options tool again to document how her experience is changing over time.

This is how Ms. B draws what she thinks it will be like to receive and live with dialysis. Is this an accurate depiction of how much risk, benefit and burden is involved in living with dialysis treatments?

After she has been on dialysis for a while, ask her to draw how it is going for her now that she understands the reality of receiving and living with dialysis. See Figure 3.

Notice the differences? Being able to "see" what she is experiencing demonstrates that we need to discuss her suffering and to make adjustments to the care plan. It might be time for a palliative care consult to evaluate if the burdens may be minimized enough so that she would be willing to continue dialysis or if because of the increasing burdens and minimal benefits, she now has a different goal of care.

PATIENT WILLINGNESS TO ENDURE THE BURDENS TO GET BENEFITS

To expand the risks, benefits and burden's drawing into a decision, you can add a column where the patient, or decision maker using the patient's values, can draw how willing the patient would be to endure the burdens of the treatment in order to get the potential benefits of the treatment. Basically, this column is asking, "Is it worth it to me to go through this (test/treatment)?"

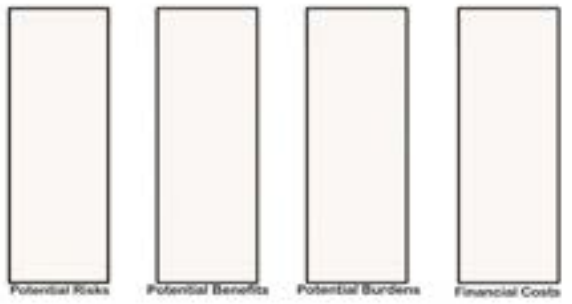
COMBINING THE OPTION ROADMAP WITH RISKS, BENEFITS AND BURDENS

Ideally, we want to make sure we are evaluating both the positive and negative potential consequences of each of the alternatives being considered. By drawing the alternatives as an Option Roadmap, not an Outcome Roadmap, we can demonstrate a complete picture of the risks, benefits and burdens of each option.[3] (Don't forget to draw the option to do nothing and the option to wait and see.) This will help patients to make better decisions based on a more thorough understanding of what they are actually choosing.

THE SLIDING SCALE FOR ACCEPTABILITY – WHERE ARE THE PATIENT'S BOUNDARIES?

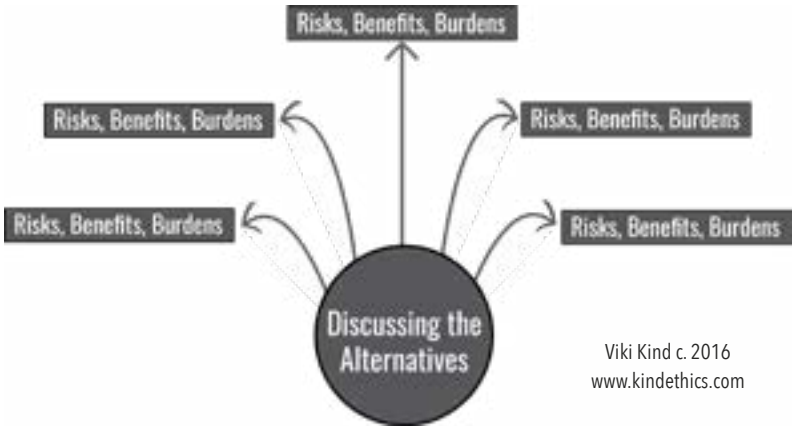
The perceived value of a specific treatment should be seen through the patient's eyes and experience. A universal question I use is, "What will it feel like and be like for (patient's name) to experience this decision?" It takes the decision out of the abstract and into the experiential. This question is exceptionally helpful to re-focus the decision-maker on the patient's suffering and needs.

FIGURE 4.
Weighing the Options - Risks, Benefits and Burdens



I use the Sliding Scale for Acceptability to establish where the patient's boundaries are for what would and would not be acceptable.[3] I use these next three sets of questions to open up the values discussion in order to make sure that the decision makes sense in the context of this patient's life. These questions will give us the criteria to use when considering, "Will this (test/procedure/treatment) achieve the patient's quality-of-life goal of (playing with my grandkids, living at home, going out into nature, etc.)?" Make sure to document the answers to these questions as they will provide helpful criteria to use for future medical decisions.

FIGURE 5.
Discussing the Alternatives



1. **What is important to me?** What makes my life worth living? These questions guide us to determine those treatments that may achieve this person's higher-level quality-of-life goals. List these worthwhile treatments in the upper section of the Sliding Scale of Acceptability. If a treatment is physiologically beneficial and may achieve the patient's goals, the treatment should be offered. Ineffective and non-beneficial treatments should not be offered even if the patient would want them.

2. What conditions would I find horrible to live with long term? What would be a fate worse than death? These questions guide us to determine those treatments that would work, but the quality-of-life outcome would not be acceptable to the patient. List these treatments in the lower section of the Sliding Scale of Acceptability.

3. What would be an acceptable level of better? I wouldn't like it, but I would be willing to live with (functional/experiential outcome). These are the boundary questions that divide the acceptable treatments/outcomes from the unacceptable treatments/outcomes. In practice, I usually use, "I wouldn't like it, but I would be willing to live with (functional/experiential outcome)," because I find it is easier for people to understand rather than "What would be an acceptable level of better?" List these treatments in the upper section of the Sliding Scale of Acceptability because although they may not be optimal, they are acceptable.

TABLE 1.

What would I want?

Acceptable Treatments and Outcomes

What could I live with?

The Gray Area

Unacceptable Treatments and Outcomes

What would I hate?

TABLE 2.

Acceptable Treatments and Outcomes

"Yes, I am okay with a feeding tube."

"I hat that I have to have a feeding tube, but I can live with it."

The feeding tube will be medically effective and will give the patient an outcome he or she is willing to live with.

The Gray Area

1. Now that this patient, with capacity, is at this moment in time, maybe he or she will want to reconsider. Give the patient good information regarding the risks, benefits and especially the burdens. Do not assume that there are only two alternatives. Ask the speech therapist about other options such as hand feeding or tube, plus little tastes of food.

2. The gray area may be where we do a time-limited trial to see if any of the possible green treatments will work. After a defined period of time, decide if the treatment should continue as a green or is now a red.

Unacceptable Treatments and Outcomes

The patient said, "No". The feeding tube is not wanted so don't do it. Even if it would be medically effective. Even if we the the person is making a mistake. Even if...

"No, never. I would never want a feeding tube."

"I don't want to live like that. I would rather die."

THE GRAY AREA

I purposely created a small gray area as a divider between acceptable and unacceptable treatment areas because in real life, there is definitely a gray zone where patients, with capacity, maybe uncertain or may change their mind. There is also the gray zone for medical uncertainty where we might use a time-limited trial to see if the treatment will actually be effective in achieving both the medical and quality-of-life goals. This time-limited trial will determine if the treatment being tried really belongs in the upper section or in the lower section.

Patients, with decisions near the gray area, may discover that what they thought would be intolerable is actually okay or what they thought they could live with is no longer acceptable. As professionals, we should not assume that patients would change their minds as a reason to not honor the patient's wishes. Lots of people are very clear and consistent about their wishes and would be angry if they discovered that their wishes weren't respected. It also illegal to go against the patient's stated refusals. (A reminder to the professionals – the patient determines these boundaries. We do not determine what would be a worthwhile outcome or an acceptable quality of life because it is not our body, not our life.)

SLIDING SCALE OF ACCEPTABILITY FOR FEEDING TUBE DECISIONS

This is a two-part decision. First, decide if the treatment will be medically beneficial. Will the feeding tube accomplish the medical goal of sustaining life? If the feeding tube can accomplish the medical goal, then move to the second part of the decision. Will the feeding tube accomplish the quality-of-life goal that the patient would say is worthwhile/acceptable? Use the three questions from earlier to determine the patient's criteria for what would be acceptable.

Table 2 is an example of how the treatment choice regarding a feeding tube might be discussed and processed within this framework.

Don't forget, everyone's Sliding Scale for Acceptability will look different. Some people will want everything done so they will have a large section of acceptable treatments/outcomes. In contrast, others may put all of the treatments you are offering in their unacceptable category. An excellent way for you to practice the tools I have shared with you is to imagine how you would demonstrate your own healthcare choices.

AUTHOR DISCLOSURES:

No relevant financial affiliations or conflicts of interest.

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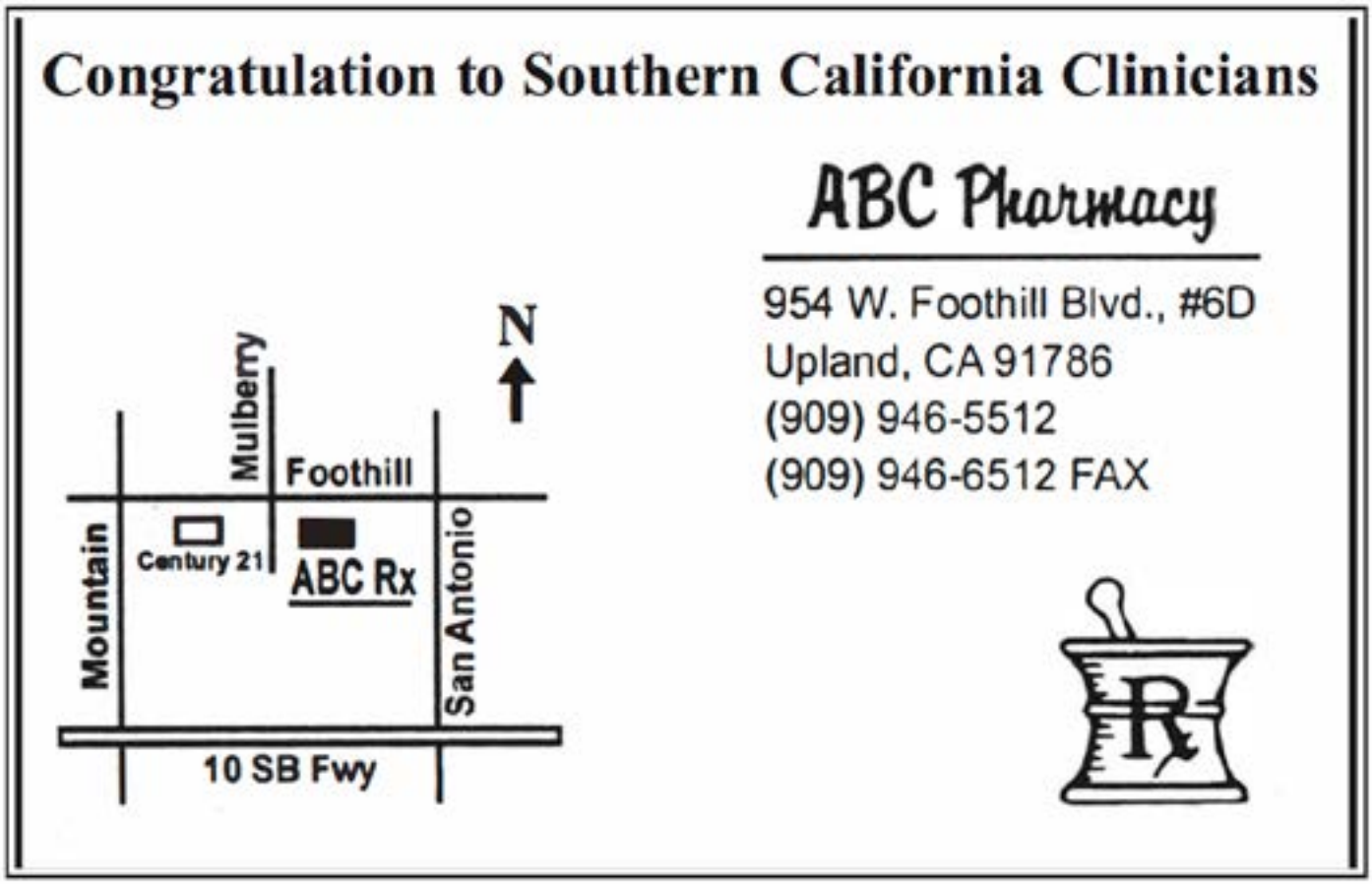

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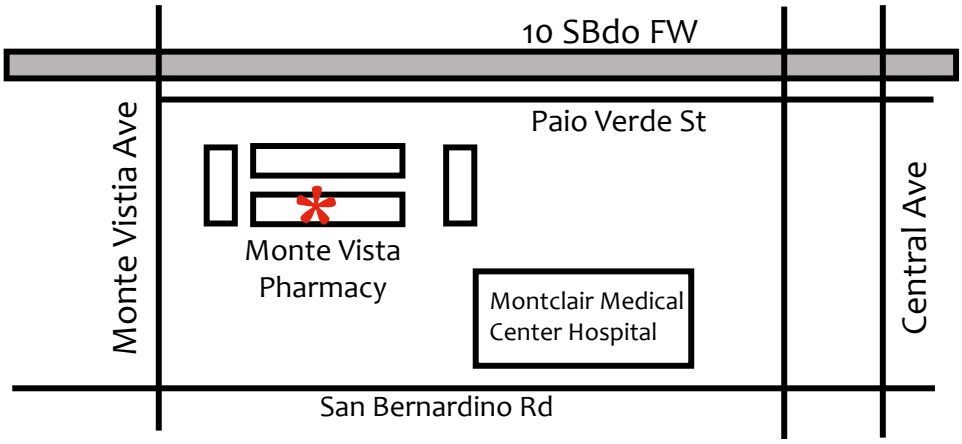

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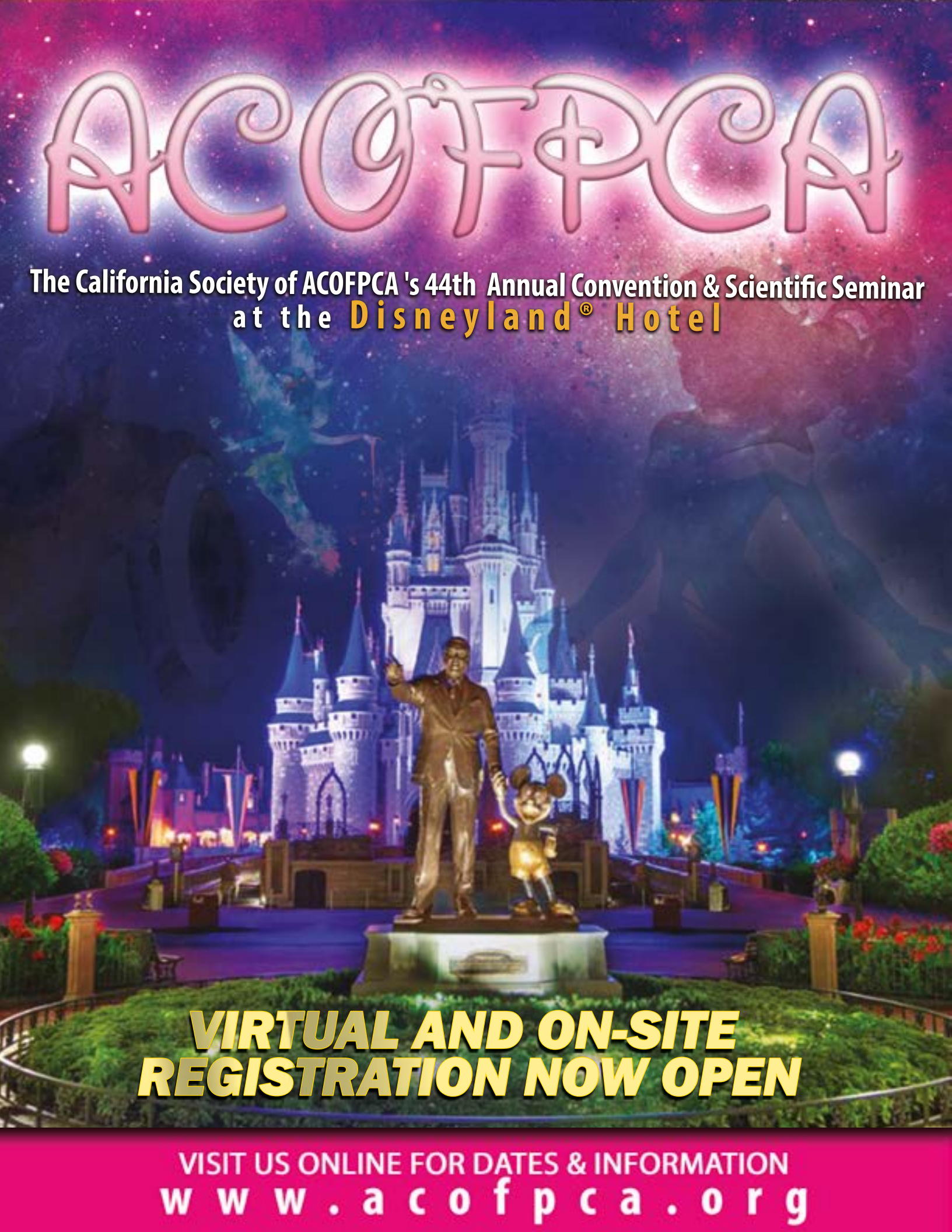
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