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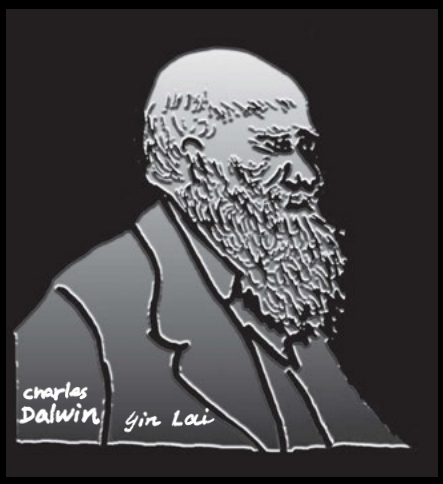

IN THIS ISSUE:

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Our Mission and Purpose

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 interesting 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, we reserve the right to peer review all articles. Articles will be reviewed by our editorial board and special consultants.

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Guidelines for Authors

On behalf of the editorial staff of the medical journal *Southern California Clinicians*, I would like to extend an invitation to you to contribute articles for publication. Articles that pertain to your medical practice, any case reports you may have, or your past clinical experiences are welcome. Articles for publication in the 2015 edition are due no later than April 30th, 2015.

1) Use a single page to show your full name, your academic degrees and affiliations, and your current address, phone number, fax, e-mail.
2) All articles must be titled.
3) Please write your article with Microsoft Office Word, double spaced.
4) Length is flexible, from 1 page to 10 pages.
5) You may include a short abstract and conclusion as you wish. Slides, tables, figures, photos or pictures are welcome. Most important is a list of references numbered in the order in which you marked in the text.
6) All articles have to be original, never been published before, reflecting your own experience, knowledge and opinion.
7) All articles, once accepted, will be peer reviewed, corrected or revised and will be sent back to you for your approval.
8) Please submit all articles in both Microsoft Word format and pdf format by email to Yin H. Lai, M.D. at his email address: yinhlai@gmail.com

Preface for this Edition

Yin H. Lai, M.D.
Editor-in-Chief

ABOUT PREVENTIVE MEDICINE

2014 is an eventful year. It's a year for Ebola, a year for influx of ObamaCare and California Medi-Cal. It's a year for ITUP (Insure The Uninsure Project) in California healthcare system.

Today, most of countries have their own health departments to be in charge of people's health, such as HHS and CDC in US, BMG in Germany, DH NHS in UK, etc. Internationally, the main organization for health of entire human being in this world is WHO. Besides, there are numerous international healthcare organizations from UN and in between two countries, such as US-UK, Germany-China ….

Furthermore, we see different levels of health care worldwide. Level I physicians perform all medical treatments of diseases which make people unable to function normally. Examples of diseases for Level I physicians to treat are, stroke, pneumonia, enterocolitis, hematemesis, hematuria, puerperal fever, gout, fractures, etc. Level II is detection of a disease-to-come. These diseases have signs and early symptoms but are usually neglected by most of patients. These include myocardial infarctions presented with intermittent chest pain, dizziness, diaphoresis and/or dyspnea. Other examples include diabetes, hypertension, peptic ulcer, and hyperthyroidism. An experienced physician on level II can give diagnosis simply by listening, observation, asking some questions, plus touching, palpitation and percussion. They usually do not depend on laboratory tests or imaging studies. Level III physicians treat any disease which has not happened yet. In other word, they are performing just preventive medicine. Public health is a study to prevent happening of any disease. A physician or a scientist who invents a vaccine is a level III health care provider. Some examples are Dr. Jonas Salk and Albert Sabin (for polio vaccines), two French microbiologists Albert Calmette and Camille Guerin (for B.C.G.), a English physician Edward Jenner (smallpox vaccine). A knowledgeable dietitian can prevent heart attack, diabetes mellitus, gout, small vessel disease and vitamin deficiency by dietary advice. Therefore a dietitian belongs to level III health care provider. The above-mentioned vaccine inventors are typical examples of level III health care providers because they prevent the occurrence of many pandemic diseases which can kill people by millions.

Actually, about two thousand years ago in ancient China, there was a famous book about medicine called " Huang Di Internal Classic " (黃帝內經). In that book, it repeatedly mentioned the importance of prevention of all illness. It already created three levels of physicians at that time:

「上醫醫未病之病；中醫醫欲病之病；下醫醫已病之病 」

The first sentence states that the level III physicians take care of diseases which are not here yet. The second sentence states that the level II physicians treat diseases which are going to happen. The third sentence states that the level I physicians treat diseases which are already happening.

In this 2014 edition of Southern California Clinicians, most of articles are emphasizing the importance of preventive medicine. If we know how to prevent a disease from happening, then the treatment will be much easier! After you finished reading all excellent articles in this volume, you will try to become a level III physician. And, this is the purpose of our editorial board to publish this medical journal for all southern California clinicians!

Editor-in-Chief Yin H. Lai, MD

LETTER TO PRACTICING PHYSICIANS
What Do You Think?

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As a family physician, I have gotten into several arguments with colleagues over the years, over the question often asked by patients, "What do you think?" or "What would you do?"

I've always thought of myself as a Consultant to patients, whose primary skill has been to interpret the vast array of information written in the foreign language of Medical-ese, into a form that can be understood by that patient. In the Family Medicine model, that has been based upon an ongoing relationship developed over time, resulting in the physician becoming a "trusted advisor". I have been very surprised over the years, to have patients come to see me to ask me about a totally non-medical issue, often a major turning point in their lives.

Why on earth would they do that? I finally started to ask them. There were variations on the theme, but generally, it was because they trusted me to tell them the truth of what I thought, that I wouldn't hesitate to give them bad news, that they respected the logic of my explanations, and they considered me one of the most educated people to whom they had access. I found that a sobering role.

I recently read an essay1 containing a passage which moved me greatly. It describes a child which developed a terminal condition, and a decision needed to be made about ongoing care, in the setting of a group conference. She writes:

"And so, with this room full of senior physicians and experts, the family turned to me, their junior resident primary care physician, and asked, "What would you do, Doctor?" The family decision followed her answer. While inevitable family anguish followed the death of the child, one year later the parents asked her to become the primary care physician of their newly born child.

Why did they do that? Because they trusted her to tell the truth about what I think most patients want to hear from us: What we think.

I believe that it is a tough time for a lot of patients. Many do not have established "trusted advisors." There is a huge repository of information on the internet on every medical subject imaginable, as some patients are fond of reminding us. Some of that information is superb, some is trash, some is agenda driven, and some is terribly outdated. You hear a lot on TV and radio. There is no rating system for any of it. How is a person to know what to do?

"Straight Talk" is a concept that is held powerfully by many. It can be a campaign slogan, such as for John McCain. It is the name chosen for an educational program for the National Council on Aging; it's even the name of a wireless company. A google search returns nearly 3 million hits. The term means that a person will tell the truth, will not sugar coat it, and has no secrets. People like this concept.

But people hate the concept that they walk out of the room from a discussion with a physician that was evasive, arrogant, or dismissive, and the doctor knows something fundamental and important that they've not told the patient. This thought, which is interpreted by

patients as a lack of integrity, causes much of the distrust with which patients view the medical profession.

I observed an episode as a young attending, where the wife of the CEO of my hospital had a skiing accident, and arrived at the ED of that hospital one night while I was attending a patient. They had a favorite orthopedist but that doctor was not available, but his new young partner was, who rushed down. I had been making small talk with the CEO and wife (an ICU nurse), who I knew, so I observed the interaction. The Orthopod went through the clinical and radiologic findings, and then discussed the possible ways of treating what was a medial meniscus tear. When he was done, they asked him "what would you do, doctor?" He then proceeded to go through the list of possible treatments, again. Amazingly, this was repeated one more time, with the patient increasingly upset. He would not answer the question. I could see a real mess brewing, so I called the original orthopedist at home, as he was a friend. He immediately called back to the ER and spoke to the CEO, then came in and spoke to them, explaining what he thought should be done. They were very happy. This painted the relationship between the two orthopedists and that hospital for a decade.

There used to be a point of view that patients "couldn't handle" the truth, that we clinicians needed to be "kind" to them, by obfuscating information. The word "paternalistic" is often used to describe that era. However, I think it is a radical mistake to think that paternalism goes along with full and complete disclosure. Withholding or obfuscating is the realm of the politician. Give strong consideration to how politicians are viewed in terms of trust and honesty. Is this the direction in which our profession should go?

On the other hand, we have to avoid the creation of false hope. There is a great deal more uncertainty about medical care than many physicians express to patients, and finding that spot between hopefulness and realism can be difficult. The problem is when it is not attempted.

Three specialties in medicine have developed around the issue of total honesty with patients revolving around end-of-life: Hospice, Palliative Care, and Bioethics. All three of these specialties require the development of great expertise in addressing the "hard" issues, and having candid conversations with people about their possible or impending deaths. However, for them, these discussions are more difficult for the patient than they would be with a "trusted advisor." These specialty physicians are, however, very skilled in bridging the gap in communication and trust.

We also have other professionals who can be superb at facilitating these conversations, such as Clergy, Social Workers, Psychologists, even Dieticians.

For those of us who have difficulty in having these very difficult but necessarily candid conversations should consider it an obligation to get one of the above involved, whether physician or not. Also consider, as those of us getting older are already finding out, that when you go into a trusted colleague's office for a consult, the most important question that you will ask is, "What do you think?"

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THE MYTH OF BREASTFEEDING JAUNDICE AND PROPOSED HOSPITAL POLICY ON KERNICTERUS

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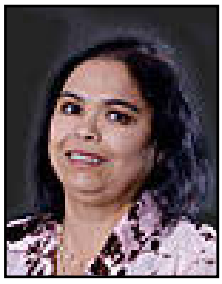

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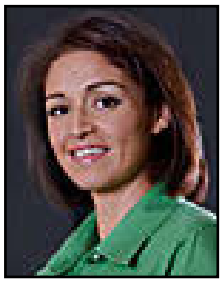

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Abstract

Since the inception of the requirements for the maternity hospitals to initiate protocols /procedures to prevent neonatal kernicterus by JCAHO and Center for Disease Control and Prevention, all maternity hospitals are using one of the several policies/protocols to comply with this requirement. However, these protocols have substituted the term " Kenicterus Prevention Policy " with broader term " Severe Jaundice Protocols ", which classifies exclusive breastfeeding as a risk factor for kernicterus. In this communication we discuss the etiology of newborn kernicterus and the risk factors for severe jaundice that may lead to bilirubin encephalopathy. Additionally the authors recommend a risk-based hospital Kernicterus policy which is consistent with the new scientific evidence.

Jaundice

Jaundice is a common occurrence in majority of breastfed newborns. The presence of jaundice in exclusively breastfed newborns is due to enhanced entero-hepatic circulation of the unconjugated bilirubin. Epidermal growth factor (EGF) in the breast milk activates the intestinal glucuronidase which dissociates the glucuronate from bilirubin in the gut and formation of the unconjugated bilirubin which is re-absorbed (1). Unconjugated bilirubin undergoes re-glucuronidation in the liver, forming direct bilirubin which is excreted in the bile, enters the intestinal tract and this cycle goes on. Bilirubin which is the end product of heme breakdown and unique to our species is a strong anti-oxidant and protects the newborn's organs from oxidative damage. The immediate precursor of bilirubin, biliverdin has anti-inflammatory properties

and beneficial to the newborn's connective tissues and immune system. The entero-hepatic circulation results in the elevation of unconjugated bilirubin and sometimes prolonged newborn jaundice. Epidermal growth factor is responsible for the development of intestinal epithelium and the immune system in the newborns. Formula supplementation of an exclusively breastfed infant or discontinuing breastfeeding results in resolution of jaundice, however the infant with a hemolytic disease or glucuronidation defect will continue with a rising bilirubin which may lead to kernicterus development. Additionally exclusive breastfeeding rate is one of the maternity hospital's perinatal core measures by JACHO and un-necessary formula supplementation will result in lower rate of exclusive breastfeeding and lower JCAHO score.

Prior to 1972 when RhoGAM was licensed in US and Canada the incidence of hydrops fetalis, stillbirth and kernictus was quite high. RhoGAM was developed in 1968 by a research team at the University of Manitoba and Ortho Pharmaceutical headed by William Pollack a British scientist. The development of RhoGAM is one of the three most significant medical discoveries of the 20th century and is credited to saving 10,000 lives a year in the United States. Although obstetricians routinely screen pregnant mothers for Rh antigen, there are a few mothers who may fall through the cracks. We took care of a one week old infant with kernicterus who was transferred to our hospital in 1976 with a bilirubin of 64 mg% due to Rh sensitization.

The etiology of neonatal kernicterus

The exact incidence of kernicterus at the present time is unknown. In a large series of the newborns, 358086, only 2 infants were diagnosed with kernicterus, who had other co-morbidities in addition to severe jaundice(2). The serum level of un-congugated (indirect) bilirubin which causes kernicterus is not known, however it is estimated to be over 35-40 mg%. Total serum bilirubin (TSB) does not constitute the best test to predict babies at risk of developing kernicterus. Unconjugated bilirubin is a lipophylic molecule and in circulation is protein-bound, therefore measurement of the free unconjugated bilirubin is more predictive of kernicterus development. However this assay is not commercially available.

Kernicterus is a devastating but preventable disease. It always results in litigation and therefore we should have access to the best tools available for inpatient and outpatient monitoring of infants who are at risk of kernicterus development. The incidence of kernicterus due to the ABO incompatibility is not known, however it is thought to be quite low. ABO incompatibility mostly occurs with blood group O and most commonly with the first pregnancy. Blood group O is more prevalent in Caucasians.

Currently glucose 6 phosphate dehydrogenase, G6PD deficiency is thought to be the most common cause of hemolytic jaundice in the newborns. The gene is more common in East-Asians, Mediteranians and African-Americans.

Physiological jaundice associated with exclusive breastfeeding may begin on the 2nd day of life and persists up to 3 weeks. The serum bilirubin varies between 5-20 mg%. The infants appear quite healthy with adequate weight gain and there is no justification to supplement with a formula or stop breastfeeding. Furthermore there is no indication for phototherapy. Kernicterus in a full-term breast-fed infant is quite rare and infants with a bilirubin exceeding 20 mg% may have a hemolytic disease or a co-morbid condition.

Pathological jaundice: This type of jaundice is due to the presence of a hemolytic disease, glucuronidation defect or hepat-biliary disorder. It is associated with rapidly rising bilirubin of 25 mg% or greater. Co-morbid conditions such as prematurity, sepsis, hypoxia, metabolic acidosis, urinary tract infection, upper GI obstruction and syndromic disorders may contribute to the development of kernicterus. Any infant with a TSB greater than 25 mg% should be carefully evaluated with a CBC, blood type, RH, Coombs test, reticulocyte count, Heins bodies in blood smear and Beutler Fluorescent spot test.

Kernicterus Prevention Policy

The medical and nursing staff should work as a team and have the knowledge and expertise of the risk factors of kernicterus development and the management of newborn jaundice.

The responsibility of the nursing staff caring of a jaundiced newborn: Evaluate the presence of any risk factors and observe for development of severe jaundice in the first 24 hours. A trans-cutaneous bilirubin, tcb, may be done at any time to ascertain the infant's jaundice level. Tcb measurements are fairly reliable for screening infants for jaundice and is preferable to serum bilirubin testing (3). However if tcb is 15 or greater a serum bilirubit determination is recommended to verify the

results. A tcb should be done on all newborns 2 hours prior to discharge and the results should be reported to the infant's physician. The attending physician will determine how soon the infant should be seen as an outpatient based on the bilirubin levels and risk factors

The responsibility of the attending physician caring of a jaundiced newborn: The attending physician should be able to differentiate between physiological and pathological jaundice. Pathological neonatal jaundice results in the rise of bilirubin at a rate greater than 0.5 mg/hour, therefore greater than 12 mg at 24 and 18 mg at 36 hours of age. The use of Bhutani's protocol and normogram which assigns the newborns to the low, intermediate or high risk zones for development of severe jaundice (4, 5, 6) should be avoided for the following reasons: (a) the protocol does not constitute a kernicterus prevention policy and is not predictive of kernicterus development following discharge. (b) The normogram is flawed because some newborns in the "low risk group" developed kernicterus following discharge. (c) The majority of the newborns in the study, 78%, never had a post-discharge serum bilirubin and the normogram was generated based on the 22% of the newborn who returned to the hospital. (d) The demographics of the newborns in the study population was 43% white, 41% black, 4% Hispanic and 4% Asians, which is quite different from our demographics. (e) The policy, instead of kernicterus prevention used a surrogate term, severe hyperbilirubinemia, which may not lead to kernicterus. Therefore this normogram does not satisfy WHO criteria for a screening test (7, 8, 9)

Treatment

Phototherapy is indicated for bilirubin equal or greater than 21 mg%. Phototherapy is not indicated for lower bilirubin levels. Breastfeeding should be continued while the infant is receiving phototherapy. All attempts should be made to avoid mother baby separation such as using a bili-blanket on the mother-baby unit.

American Academy of Pediatrics recommends a follow up of all newborns in 1- 3 days for careful evaluation of jaundice status and to prevent the tragedy of kernicterus development.

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AMBULATION AFTER TOTAL KNEE ARTHROPLASTY:

A Comparison of Prognosis Following Adductor Canal Block vs. Femoral Nerve Block

Authors: Michael Wong, D.O.
Tyler Gouvea, OMS III

Introduction

A recent topic of interest in the field of anesthesia is total knee arthroplasty/replacement (TKR), the different approaches currently available and their effects on ambulation. The two main techniques that have been studied extensively are the adductor canal block (ACB) and the femoral nerve block (FNB). This article will review current anesthesia research regarding the management of TKR and compare the two techniques to each other, as well as analyze them individually in terms of their relation to ambulation. Aspects of ambulation that were studied include: strength of quadriceps[1,2], range of motion in knee flexion[3], distance ambulated[4] and time taken to ambulate a fixed distance[2,5]. Correlations between strength, range of motion, distance walked, and timed-up-and-go test and practical ambulation are not directly established. However, these studies are a step towards optimizing recovery time through choice of anesthesia delivery and minimizing immobility, which prevents risks for the patient.

Background

The FNB targets the femoral nerve, which originates from nerve roots L2-L4 and has both a sensory and a motor component. The motor component innervates four muscles—the iliopsoas, pectineus, sartorius, and quadriceps femoris—while the sensory component gives rise to the anterior cutaneous branches and the saphenous nerve[6]. Medial to the Femoral Nerve are the Femoral Artery and Vein, separately bundled in the Femoral Sheath. All three pass deep to the Inguinal ligament and emerge inferiorly. Deep to the Femoral Nerve is the Iliopsoas muscle, and both are covered by the iliac fascia[7].

The FNB technique begins with positioning the patient supine with the thigh abducted and externally rotated. Using ultrasound at the femoral crease, the Femoral Nerve is visualized superior to the Iliopsoas muscle and lateral to the Femoral Artery. The needle is inserted lateral to medial in the plane of the ultrasound transducer until it penetrates the iliac fascia, at which point local anesthetic agent is delivered[7].

The ACB targets the Saphenous Nerve, a branch of the Femoral Nerve that is located in the adductor canal along with the Femoral Artery and Femoral Vein. The Adductor Canal is bound medially by the Sartorius muscle, laterally by the Vastus Medialis muscle, anteriorly by the Vastoadductor membrane, and posteriorly by the Adductor Longus and Magnus muscles[6].

The ACB technique begins with the patient positioned similarly to the FNB in order to gain access to the medial thigh. With the ultrasound transducer at the mid-thigh, the Saphenous Nerve and Femoral Artery can be visualized running deep to the Sartorius muscle. The needle is inserted from anterior to posterior in the plane of the transducer until it is deep to the Sartorius muscle. Once it is localized to the Saphenous Nerve and Femoral Artery, the local anesthetic agent is delivered[7].

Strength

The first aspect of ambulation analyzed was strength. In a study published January 2014 in Anesthesiology1, the strength of patients' quadriceps was measured by dynamometer in kilograms-force (kgf) units. This study compared 93 patients receiving TKR, with 46 receiving ACB, using 15ml Bupivacaine 0.5% and 5 µg/ml Epinephrine, versus 47 receiving FNB, using 30ml Bupivacaine 0.25% and 5 µg/ml Epinephrine. Six to eight hours after the surgery, the mean quadriceps strength in patients who received the ACB was 6.1 kgf, compared to patients who received the FNB who had a mean of 0 kgf (Table 1). The difference was statistically significant with a P value of <0.0001. However, a note of interest was that 24 hours post-op, the ACB patients went on to have a decrease in mean strength from 6.1 to 3.5 kgf, while the FNB patients had an increase in mean strength from 0 to 2.8 kgf. Although the group with the ACB had decreased mean strength relative to 6 to 8 hours post-op, they still had greater strength than the group with the FNB.

Another study done in November 2013 in Regional Anesthesia and Pain Medicine2 also compared the quadriceps strength in those who received ACBs and FNBs. The study was double-blind, randomized and controlled, measuring percentage of muscle contraction in 48 participants, 22 in the adductor group and 26 in the femoral group. Both groups were given a bolus of 30ml Ropivacaine 0.5% then 8ml/hour Ropivacaine 0.2% for 24 hours. Patients who received the ACB had 25% of the baseline maximum voluntary isometric contraction 24 hours after surgery, compared to only 18% in those who received FNB (Figure 1). The difference in these two groups 24 hours post-op was statistically significant with a p-value of 0.004 within a 95% confidence interval.

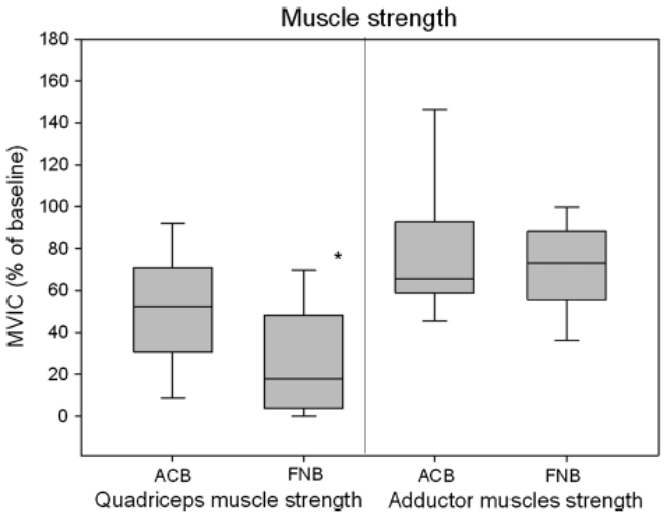

Figure 1. Strength in Quadriceps and Adductor with ACB vs. FNB measured in % of baseline Maximum Voluntary Isometric Contraction (MVIC)2

Time of Follow-up	ACB N = 46	FNB N = 47	Difference: ACB-FNB (95% CI)	Test of Equal Medians: *P* Value (Holm–Bonferroni)*
Operative leg				
Preoperative, kgf	15.6 ± 8.5 12.3 [9.6, 20.2]	14.8 ± 8.2 11.6 [8.3, 20.1]	0.8 (–2.7 to 4.2)	0.9999
Postanesthesia 6–8 h, kgf	7.3 ± 5.4 6.1 [3.5, 10.9]	2.2 ± 3.8 0.0 [0.0, 3.9]	5.2 (3.1–7.2)	<0.0001
Postanesthesia 24 h, kgf	3.9 ± 4.2 3.5 [1.1, 4.4]	4.0 ± 4.0 2.8 [1.1, 6.8]	–0.1 (–1.9 to 1.6)	0.9999
Postanesthesia 48 h, kgf	2.2 ± 2.9 1.8 [0.0, 3.3]	2.8 ± 3.2 1.7 [0.0, 4.1]	–0.6 (–1.9 to 0.7)	0.9999
Nonoperative leg				
Preoperative, kgf	18.5 ± 9.1 16.7 [11.6, 24.4]	18.3 ± 9.2 16.9 [10.7, 27.4]	0.2 (–3.6 to 4.0)	0.9999
Postanesthesia 6–8 h, kgf	15.8 ± 7.6 14.4 [9.9, 21.3]	16.2 ± 10.3 13.9 [8.1, 25.4]	–0.4 (–4.4 to 3.6)	0.9999
Postanesthesia 24 h, kgf	16.7 ± 7.4 15.7 [10.2, 22.6]	17.8 ± 9.0 16.9 [10.1, 25.4]	–1.1 (–4.6 to 2.5)	0.9999
Postanesthesia 48 h, kgf	16.7 ± 7.8 15.1 [12.0, 22.0]	18.5 ± 11.8 16.4 [9.2, 26.3]	–1.8 (–6.2 to 2.6)	0.9999

Results presented as mean ± SD, median [first, third quartiles].
* Holm–Bonferroni adjusted $P < 0.05$ is considered statistically significant.
ACB = adductor canal block; FNB = femoral nerve block; kgf = kilogram-force unit.

Table 1. Strength of Quadriceps with ACB vs. FNB 1

Both of these studies indicate that there is a significant gain of quadriceps muscle strength postoperatively in patients who received ACBs relative to those who received FNBs. However, it is uncertain whether that benefit is transient, as demonstrated in the 2014 study1, or lasting at least 24 hours, as was shown by the 2013 study2. In order to address this, a study conducted with a longer time frame post-op to measure outcomes is needed to determine if any longer-term (48 hours to 7 days) benefit is gained by one block over the other. Another topic of consideration that arose in the 2014 study1 was that the FNB group had 3 patients who "buckled" while ambulating, which was attributed to quadriceps weakness. Although not an objective strength measurement, there were no patients in the ACB group who "buckled." A further study with a larger sample size is needed to assess whether this "buckling" is a legitimate fall risk with a demonstrably significant difference in the groups.

Range of Motion

Another aspect of ambulation is range of motion (ROM) of the joints involved, particularly the lower extremity, in this case focusing on the knee status post TKR. A prospective, randomized and controlled study conducted at the Osaka University, Graduate School of Medicine in Japan, May 2013 in The Journal of Arthroplasty3 assessed ROM in 60 patients, 30 who received continuous femoral nerve block (CFNB) with a single injection tibial nerve block versus 30 who received a continuous epidural anesthesia (CEA), all of which used Ropivacaine 0.3%.

Patients who received a CFNB could passively flex their knee to 120 at a mean of 8 days postoperatively, as opposed to patients who only received a CEA who needed an average of 15 days to achieve the same ROM. The difference in time to full 120 was about 6.5 days, with a 95% confidence interval and p-value <0.001. Even prior to attaining the full passive ROM, on Post-Op Day (POD) 4, patients in the CFNB arm had achieved a mean of 100 ROM, compared to patients in the CEA arm, who had only achieved 90 . Even at this point, the difference between these groups was statistically significant, with the p-value <0.001. Therefore there was a significant gain in degrees in ROM in patients who received the CFNB, even relatively early (POD 4) in the post-operative course.

Unfortunately, the study is not purely in support of CFNB because the arm of the study that received CFNB also received a tibial nerve block, thus confounding the comparison. Additionally, a unique aspect about this study was that the ROM parameters were set to 120 rather than the typical 90 that many other studies use. The researchers explained that in Asian and Middle Eastern cultures, squatting, kneeling and sitting with one's legs crossed were far more common activities, compared to Western cultures, where patients are more commonly sitting in chairs, so the norm of 90 would not be sufficient to evaluate their population. Finally, due to the institution's policies concerning patient safety, the study was not double-blinded and did not contain a placebo group.

Distance & Time

Further studies have examined ACBs and FNBs, focusing instead on the distance or time. One method involved measuring the distance ambulated by patients after receiving the different blocks. The first study, published July of 2013 in Regional Anesthesia & Pain Medicine4, examined the distance that patients could ambulate post-operatively status-post TKR. Nearly 300 patients were included over an 8 month period, divided into three groups exploring three different modalities of anesthesia: local infiltration analgesia (LIA), LIA plus adductor canal block (LIA plus ACB), continuous femoral nerve block (CFNB). The LIA was accomplished with 150ml Ropivacaine 0.2%, 30mg Ketorolac, and 0.6mg Epinephrine. The LIA plus ACB used 20ml Ropivacaine 0.5% and the CFNB used 30ml Ropivacaine 0.2% then 5ml/hour Ropivacaine 0.2%. The average distance that patients were able to ambulate on POD 1 that received LIA plus ACB was 30 meters. Those who only received LIA could only walk an average of 20 meters while those that received CFNB averaged 0 meters. While the results displayed a statistically significant difference in these modalities of anesthesia delivery, with a p-value <0.001, the inclusion of LIA presented a confounding variable in a straight comparison between adductor and femoral nerve blocks. The study was also a retrospective, non-randomized and observational cohort study and thus did not provide Grade A evidence.

Another method examined the time it took for patients to ambulate a fixed distance using the Timed-Up-and-Go (TUG) test. The TUG test was first developed and described in a study in February 19918 with a cohort of 60. To conduct the TUG test, the patient starts seated in a chair, with an observer who has a stopwatch. The observer starts the time when the patient gets up out of the chair. Once the patient has risen from the chair, they are to walk 3 meters, turn around, return to the chair and

sit down, at which time the stopwatch is stopped and the time measured.

Discussion

A double-blinded, randomized study conducted March 2012 in Acta Anaesthesiologica Scandinavica5 used the TUG test to compare 71 patients who received either ACB using 30ml Ropivacaine 0.75% or an ACB placebo using isotonic saline. Patients receiving the true ACB took an average of 36 seconds to complete the TUG test 24hr post-operatively, compared to the placebo group who took 50 seconds, with a p-value 0.03. After the TUG test was completed, both groups received a bolus of 15ml Ropivacaine 0.75% and two hours later—at 26 hours post-operatively—the groups completed another TUG test (Figure 2). The ACB group took 33 seconds and the placebo group took 41 seconds to complete, with p-value 0.21, demonstrating a less significant difference between the groups than at 24 hours.

Another study published November 20132, which was referenced earlier in the discussion about quadriceps strength, also utilized the TUG test in comparing the ACB and FNB. 22 patients in the ACB arm had an average TUG test of 37 seconds 24 hours post-operatively, while 26 patients who received the FNB had an average of 39 seconds. With a p-value 0.59, the study did not demonstrate a significant difference between the two groups in terms of TUG performance.

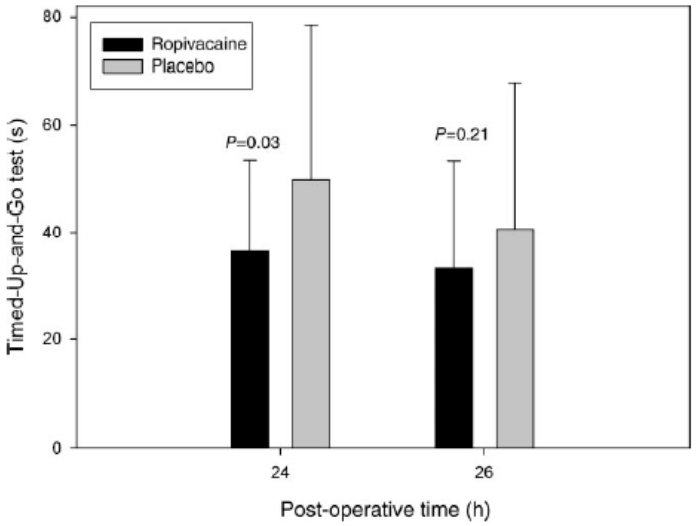

Figure 2. Mean times of completion of the TUG test in patient's receiving ACB with 30ml Ropivacaine 0.75% vs. Placebo (isotonic saline) at 24 hours Post-Op as well as at 26 hours after both receiving a bolus of Ropivacaine 0.75% following the 24 hour measurement5.

Conclusion

In compiling the recent research comparing different anesthesia modalities and ambulation of patients status-post TKR, there is support that ACBs result in greater quadriceps strength post-operatively1,2. ACBs also result in faster walking times for fixed distances, evaluated using the TUG test, compared to a placebo5. However, there is no significant difference between the ACB and the FNB in the TUG test 24 hours post-operatively2. Still, patients who received the ACB walked a considerably longer distance on POD 1 than those with CFNB, although this study was complicated by the fact that the patients in the ACB arm also received LIA4. Additionally, the CFNB resulted in greater ROM compared to no regional block3.

An interesting point of consideration remains after discussion of the current literature. Even though these studies all examine objective measures such as strength1,2, ROM3, distance traveled4, and time to travel a fixed distance2,5, it has yet to be established how these measurements correlate to patient outcomes in terms of health and safety. In a clinical setting, significant concerns include deterring the consequences of immobility, such as prophylaxis and prevention of deep vein thrombosis (DVT) and pulmonary embolism (PE) formation, as well as ensuring safe ambulation, assessing fall-risk and employing proper fall precautions. Additionally, there was a limited scope of complications evaluated. Although one study found no significant difference between the two types of blocks in terms of nausea/vomiting, pruritus, patient satisfaction or hospital stay, other complications such as rates of hematoma, infection and DVT were not examined1. Further research will need to be done before it can be determined how these results can be applied to actual anesthesia practice.

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DIFFERENTIAL DIAGNOSIS OF MEDIASTINAL AND HILAR LYMPHADENOPATHY

Necrotizing Granulomatous Interstitial Pneumonia with Bilateral Mediastinal and Hilar Lymphadenopathy Masquerading as Metastatic Carcinoma ---- A Case report

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Abstract

We report an unusual case of interstitial lung disease in a 59 year-old male smoker, who presented to the emergency department complaining of dyspnea. Computer tomography (CT) of his chest showed extensive bilateral nodular pulmonary infiltrates associated with mediastinal and hilar lymphadenopathy. This prompted a thorough work up of the pulmonary system because of suspected metastatic malignancy. Subsequent surgical wedge resection biopsies of lung revealed extensive destructive parenchymal lung injury, variably reminiscent of interstitial pneumonia, pulmonary fibrosis, brochiolitis obliterans organizing pneumonia (BOOP), desquamative interstitial pneumonia, and necrotizing granulomas. The patient's history was significant for occupational exposure to fumes in a rubber factory and chronic obstructive pulmonary disease (COPD). A microbiological culture of sputum was positive for Pseudomonas aeruginosa. All other cultures studies and serologic tests for a variety of immunologic disorders were negative. These findings warrant inclusion of inflammatory, infectious, idiopathic, as well as occupational lung disorders in the differential diagnostic consideration in patients presenting with nodular lung infiltrates suspected of metastatic carcinoma.

Introduction

Interstitial lung disease represents a large group of disorders that may cause progressive fibrosis of lung parenchyma. It may be idiopathic or caused by long-term exposure to a variety of inflammatory, infectious, or hazardous material. Occupational interstitial lung disease (ILD) has long been known to exist in industries such as construction, mining, textiles, ceramics, rubber and tire [1]. The most well characterized pathologies are those resulting from asbestos and silica, followed perhaps by coal and beryllium [1].

We present a case of interstitial lung disease in a 59-year-old male smoker and tire factory worker with history of COPD who presented to the emergency department with progressively worsening dyspnea accompanied by hilar and mediastinal lymphadenopathy suspected of metastatic malignancy. Biopsies of lung lesions however showed a variegated pattern of lung injury dominated by interstitial pneumonia and necrotizing granulomatous inflammation. Past medical and social history of smoking and occupational exposure to rubber fumes at the tire factory warranted consideration of involvement of chemical toxicity, possibly exacerbated by an infectious process may have contributed to the pathogenesis of the spectrum of histopathologic features observed in this patient's interstitial pneumonia. Rubber fumes have only rarely been described as a causative or contributing factor significant lung injury.

Case Presentation

The patient is a 59 year-old male who presented to the Emergency Department with the chief complaint of "difficulty breathing of several months duration" which worsened on the day prior to ED presentation. Past medical history was significant for multiple recent COPD exacerbations. Social history was significant for a 30-pack year smoking history with cessation four years prior as well as an occupational exposure to rubber fumes and dust at a tire factory.

The patient's vital signs were as follows: Temperature 98.2°F, pulse 85/min, respiratory rate 20/min, and blood pressure 109/74. The physical examination revealed an obese male, alert and oriented to person, place, and time, but in mild distress. The abdomen was soft, non-distended, with no guarding or rebound tenderness but generalized tenderness to palpation. Respiratory exam revealed bilateral rales and crackles, most notably in the lung bases. There were no other significant findings in the other systems.

Laboratory findings included a leukocytosis of 19.0 x 103/mL with 58% segmented neutrophils, 18% band neutrophils, and 4% lymphocytes, and 20% monocytes; serum sodium 136 mEq/L, serum potassium 3.6 mEq/L; serum chloride 102 mEq/L, CO2 27 mmol/L, BUN 18 mg/dL, creatinine 0.83 mg/dL, AST 41 U/L, ALT 48 U/L, Alkaline phosphatase 80 U/L, Lipase 54 U/L, Total protein 7.5 g/dL, Albumin 3.0 g/dL. The patient's urine was positive for a large amount of blood and white blood cells, and was positive for leukocyte esterase and bacteria. On admission, the arterial blood gas analysis was as follows: pH, 7.43; pCO2, 58 mmHg; pO2, 54mmHg; and HCO3-, 37 mEq/L.

one microbiological culture of sputum expectorate grew scant light colonies of Pseudomonas aeruginosa. All other routine cultures, including mycobacterial, of sputum were negative for other microorganisms. Serologic tests for routine microorganisms were likewise negative. Anti-neutrophilic cytoplasmic antibody (ANCA) test was not performed during this hospitalization.

A CT with contrast of the chest was performed (figure 1). The scan revealed extensive bilateral patchy infiltrates throughout both lung fields as well as bilateral bronchiectatic changes and mediastinal and hilar lymphadenopathy. Because of the latter imaging study findings, video-assisted thoracoscopic lung biopsies were performed to rule out malignancy.

Pathologic Findings and Clinical Course

The specimen submitted for pathological evaluation consisted of three wedge-shaped lung biopsies, two from upper right lobe segments and one from lower right lobe segment. There were no grossly discernible lesions. Histopathologic sections revealed multiple nodular areas of parenchymal and interstitial fibrosis accompanied by an occasional, centrally necrotizing, granulomatous lesion (figure 2). Chronic and acute inflammation was present. Patchy deposits of hemosiderin-like pigment granules and parenchymal extravasation by blood were consistent with recent and remote hemorrhage. Occasional bronchioles were obliterated by loose connective tissue consistent with brochiolitis obliterans organizing pneumonia (figure 3), focally accompanied by necrotic debris, mucus, neutrophils, and macrophages. Also present were pigment bearing intra-alveolar macrophages reminiscent of desquamative interstitial pneumonia. Thick-walled vascular structures were seen occasionally (figure 4), consistent with pulmonary hypertension.

Discussion

Interstitial lung disease is a well-recognized disorder of lung with complex pathogenesis necessitating a close multidisciplinary correlation of morphologic, clinical, and radiographic approach to diagnosis and treatment. The prevalence of interstitial lung disease is estimated to be anywhere from 6-32 per 100,000 people [6]. Case controlled studies have consistently demonstrated that these cases of ILD are highly correlated to occupational and environmental exposures [6]. Some cases are preventable in professions that deal with chemical fumes, solvents, dusts, and particulate matter. However, neither the pathophysiology nor the epidemiology of many interstitial lung diseases are well described.

The driving factor of lung damage is postulated to be pathological healing secondary to repetitive lung insults. Recent research suggests the mechanisms behind the abnormal healing processes may include a combination of alveolar epithelial endoplasmic reticulum stress and telomerase dysfunction [5]. This abnormal healing results in a myriad of findings including chronic inflammation, fibrosis, and obliteration of normal lung parenchyma.

The epidemiology of many interstitial lung diseases is not well delineated. There are many confounding factors that make data collection difficult, including lack of physician recognition, lag time of decades between exposure

and diagnosis, subjection to multiple inciting agents, concurrent exposure with smoking, genetic variation in susceptibility, and characterization of occupational lung disease as idiopathic. [1] However, it is now well accepted that the likelihood of developing idiopathic pulmonary fibrosis is influenced by environmental exposure to a variety of injurious agents including occupational toxins, smoking, and viruses [1,3,4].

In our patient, the spectrum of pathologic lesions, including nodular foci of interstitial and parenchymal fibrosis, obliterative bronchiolitis with organizing pneumonia, and necrotizing granulomatous inflammation warrants consideration of involvement by multiple etiologic factors in the pathogenesis of his lung injury. The patient's prolonged history of exposure to toxic agents, cigarette smoke and rubber fumes, were most probably major contributing factors.There is sufficient evidence for an excess occurrence of stomach and lung cancer among rubber workers [7]

Distinction these variably disabling lung interstitial diseases from cancer may at times clinically and radiographically challenging. Because of considerable differences in prognosis and treatment, careful questioning regarding past social and occupational history is essential in order to include these disorders in the differential diagnostic consideration.While recent research has begun to elucidate the underlying causes of these lung diseases, we are far from the point of medical life-saving intervention. In some cases, such as idiopathic pulmonary fibrosis, the median survival is only 4-5 years [8], hence the importance of preventing exposure to agents suspected of causing these interstitial pulmonary disorders cannot be underestimated.

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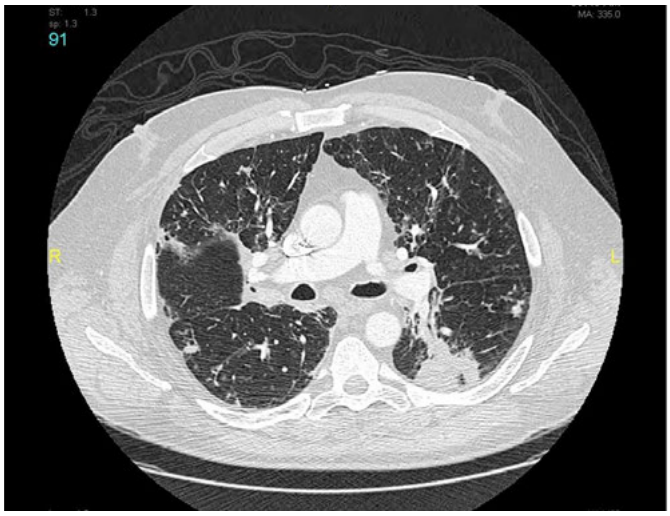

Figure 1. CT of the chest with contrast showing pulmonary infiltrate with mediastinal and hilar lymphadenopathy.

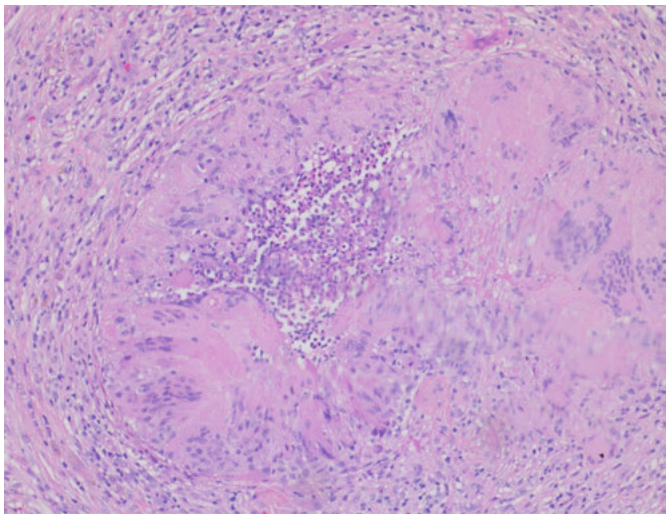

Figure 2. Centrally necrotizing granulomatous lesion identified in histologic sections from the lung biopsies.

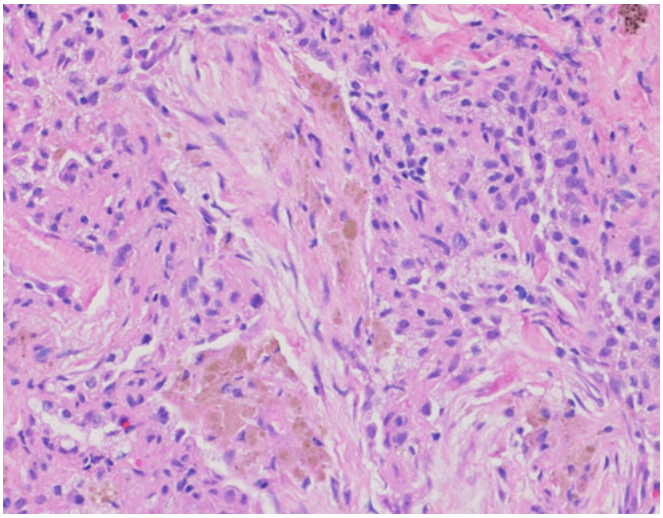

Figure 3. Loosely arranged connective tissue containing deposits of hemosiderin-like pigment granules displace portions of lung parenchyma reminiscent of organizing pneumonia.

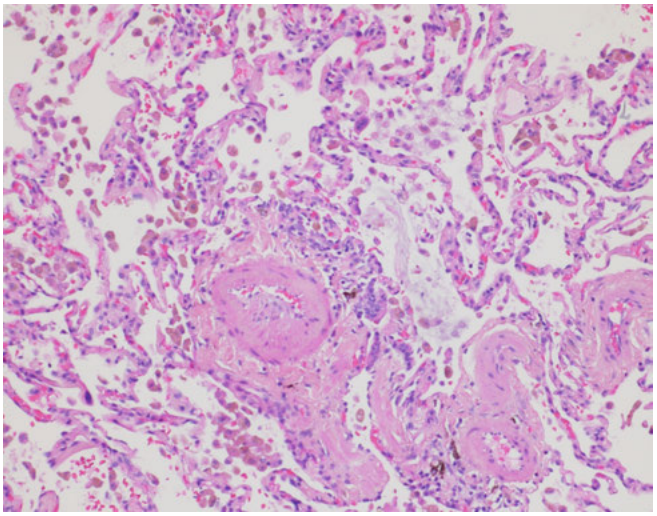

Figure 4. Occasional thick-walled vascular structures are consistent with pulmonary hypertension.

CHILDHOOD OBESITY IN THE UNITED STATES AND HOW IT RELATES TO FAST FOOD CONSUMPTION AND THE BUILT ENVIRONMENT

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Dramatic increases in the prevalence and incidence of childhood obesity in the United States of America is an increasing cause of national concern. According to the Centers for Disease Control and Prevention, childhood obesity has more than doubled in children and tripled in adolescents within the last thirty years [1]. In fact, more than 17% of children and adolescents are classified as obese, which is defined as a body mass index (BMI) greater than the 95th percentile. An alarming one in three children classify as overweight, having a BMI greater than the 85th percentile [1]. This epidemic warrants our concerns because of its devastating medical and psychological complications that begin in childhood and exacerbate through adulthood. Childhood obesity is a multisystem disease causing pulmonary, orthopedic, gastrointestinal, cardiovascular, gynecologic, endocrinologic, renal, neurologic, and psychosocial complications [2]. Moreover, there are also considerable financial burdens from a national economic standpoint. Childhood obesity alone is estimated to cost $14 billion annually in direct health expenses [3]. Thus, there is a much-needed effort to understand the causes of childhood obesity and identify prevention strategies within the medical, political, and environmental arenas.

It is well recognized that both genetic and environmental factors contribute to the development of obesity. Some argue, however, that the exponential increase in obesity prevalence among a genetically stable population within the last three decades strongly suggests that behavioral and environmental factors, such as poor nutrition and lack of physical activity, may be playing a much larger role than genetics [4]. Some of these factors can be attributed to the significant changes in society that have occurred over the same three decades over which the obesity epidemic has developed. For instance, having both parents work, eating more meals outside the home, and a changing school food environment, alongside the changes in the physical design of neighborhoods directly affects what children eat, where they eat, how much they eat, and the amount of energy they expend [5]. Therefore, understanding these contexts and how they can be modified is essential for reduction in childhood obesity.

Fast food is becoming an increasingly large component of the American diet. To put things in perspective, the presence of fast-food restaurants in the US increased seven fold between the 1970s to early 2000s [6]. Adolescents are certainly frequent visitors to these venues, averaging two visits to a fast-food restaurant in a single week [7]. Fast food is high in fat and energy, and although many fast-food chains have expanded their menus to include "healthier" options, hamburgers and french fries continue to be the primary source of revenue [8]. These foods are high in saturated fats, which have adverse effects on cardiovascular health [9]. In contrast, foods that are rich in unsaturated fats, including vegetables and fish, can decrease the risk for the same diseases. Moreover, carbohydrates, particularly in the form of refined foods (e.g., breads, potatoes, and soft drinks), have a high glycemic index and can potentially stimulate hunger and cause overeating. A high glycemic index diet has also been linked to risks for cardiovascular disease, type 2 diabetes mellitus, and central adiposity [10]. In addition, sugar-sweetened beverages (SSB) have been distinctively studied, in part because of the rapid increase in their rate of consumption among youth. A recently published randomized trial involving over 220 overweight and

obese adolescents who regularly consumed SSB showed that replacing these drinks with non-caloric beverages led to decreases in weight compared to the group who did not receive this intervention [11]. Another study showed that even young children between the ages of 2 through 5 who regularly consumed SSB demonstrated both prospective and cross-sectional correlations with higher BMI z scores [12]. Although fast-food restaurants are surely not the only source of saturated fats, carbohydrates, and sugary drinks in a young person's diet, the fast-food industry has undoubtedly helped make these foods easily accessible and desirable.

The answer to the question as to why fast food outlets have gained considerable popularity in recent decades is complex and multifaceted. Certainly, the commercial environments that surround youth and families heavily influence their purchasing and consumption behaviors. More often than not, these consumers compromise long-term health for the sake of taste, cost, and convenience [5]. In addition, there is a growing body of literature that suggests that another important and potentially modifiable factor related to childhood obesity is the built environment, including access to facilities and neighborhood design. Neighborhoods that have increased amounts of vegetation compared to areas with less greenery have lower rates of childhood obesity, presumably due to increased physical activity and time spent outdoors [13, 14]. A similar difference in childhood obesity rates is observed in communities where residents are in close proximity to supermarkets compared to areas where residents live in close proximity to convenience stores or fast-food outlets [14]. When food availability becomes constrained to small convenience stores that have limited, high-priced selections, fast food becomes a more convenient, inexpensive, and sometimes, sole option. In contrast, adult studies show that supermarkets are positively correlated with consumption of fruits and vegetables and inversely associated with obesity [15]. Thus, it is important to acknowledge that the way we build our communities heavily influences what our children eat, and how they expend energy. With this recognition, we have the potential to lower childhood obesity rates in this country.

The increase in childhood obesity has reached unprecedented numbers, and demands we understand what modifiable factors have led to this growth. For instance, the growth of the fast food industry has contributed to the easy accessibility of foods that are rich in fats and carbohydrates to our nation's youth. This is especially true in neighborhoods that have a higher representation of fast food restaurants than supermarkets or even greenery. Thus, avenues of change may lie within the fast food industry and neighborhood design. Although these are just a few factors contributing to the childhood obesity epidemic in this country, even small changes may have significant impacts.

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MANAGEMENT OF TYPE 2 DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS

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Previously, Type II Diabetes Mellitus was rarely seen in children and adolescents. However, the increase in childhood obesity has lead to an increasing prevalence of Type II Diabetes in this population. Most commonly, it is seen in the ages of 10-19 years old, while being less commonly seen in children under the age of 10. Such a young age of onset of diabetes increases the risk for complications and therefore it is very important to manage aggressively. Managing T2DM in the pediatric population comes with its own set of challenges and therefore requires a slightly different approach compared to adults. Treating children with T2DM requires a family-centered approach due to the role of the family in impacting the health outcomes of these children. Most of the information that we have presently regarding the management of these patients comes from the TODAY study (Treatment Options for type 2 Diabetes in Adolescents and Youths).

Screening of T2DM should be done in asymptomatic children who have a BMI ≥ 85% and 2 risk factors such as signs of insulin resistance, family history of T2DM, maternal gestational diabetes, or being a member of a high risk ethnic group (Native American, Hispanic, Pacific Islander, Asian, or non-Hispanic black). Diagnosis of T2DM is confirmed with a Hemoglobin A1c≥ 6.5%, FPG≥126 mg per dL on two separate occasions, or random venous plasma glucose≥ 200mg/dL in a patient with symptoms of hyperglycemia.

After a diagnosis of T2DM is made, the initial step in management includes non-pharmacological management as well as pharmacological management. Non-pharmacological treatment primarily takes the form of counseling patients on lifestyle changes in order to improve insulin sensitivity. These lifestyle changes include weight loss and physical activity. Depending on the age of the patient and whether the child is still growing, a weight maintenance or weight reduction approach may be taken. Those patients whose BMI dropped from an average of 43.5 to 39.3 had an average drop of HbA1c from 8.8% to 7.4%.

Treatment of obesity in children and adolescents is done in four stages beginning with stage 1 and advances depending on the progress of the patient. The first stage begins with prevention and starts with healthy eating, increasing activity, decreasing the amount of sugar-sweetened drinks, and limiting television watching. It is critical for the whole family to be involved in these lifestyle changes in order to be successful. If there continues to be no progress after 3-6 months, then it would be appropriate to advance on to stage 2 which requires more structure for the patient. Stage 2 includes providing meal plans for patients with assistance from a dietician, decreasing television watching to less than 1 hour a day, and ensuring physical activity of at least 1 hour a day with activity logs. Office visits should be once a month and include motivational interviewing.

If despite these measures, the patient fails to progress, then the patient should be advanced to stage 3 which includes a multidisciplinary approach including behavior counselors, psychologists, and social workers. Initially,

the patient should come for weekly visits for 8-12 weeks in order for this method to be effective. These visits may be in the form of group visits for efficiency.

For severely obese adolescents, where a multidisciplinary approach has already been attempted, the physician should tertiary care intervention. Medications to stimulate weight loss may be used in adolescents to aid in weight loss, examples being Orlistat and Sibutramine. Orlistat is a saturated derivative of lipstatin which is a potent natural inhibitor of pancreatic lipases. It can be used in adolescents aged 12 and up. Sibutramine is an SSRI and may be used in adolescents older than 16 years of age. A very low calorie diet should be started. Gastric bypass or gastric binding may be considered as well. Criteria for gastric bypass include a BMI greater than 40 with a medical condition or a BMI greater than 50 with or without a medical condition. This should only be considered in female adolescents greater than 13 years of age, or males greater than 15 years of age. However, at least 6 months of behavior-based treatment should be attempted before these measures are to be considered.

Along with non-pharmacological measures, pharmacological treatment should be started in patients diagnosed with Type 2 Diabetes Mellitus as well. FDA approved medications for use in children and adolescents are metformin and insulin. Thiazolidinediones such as rosiglitazone and pioglitazone are not yet FDA approved for use in children due to cardiovascular concerns with rosiglitazone and concerns of bladder cancer with pioglitazone. There are also concerns of skeletal effects with both medications. Sulfonylureas are not used in children and adolescents due to studies showing weight gain in participants.

In order to determine the best course of action for treatment of Type 2 Diabetes Mellitus, the TODAY study evaluated treatment failure in 699 youths aged 10-17 years who had a diagnosis longer than 2 years and a BMI greater than 85%. Treatment failure was defined as HbA1c≥ 8% for at least 6 months or metabolic decompensation requiring insulin for 3 or more months. According to the study, there was more treatment failure in this patient population compared to adults (45.6%). As explained in the study, this was not due to non-adherence to the treatment. Treatment failure was evaluated in patients who were treated with metformin alone, metformin with lifestyle modification, and metformin with rosiglitazone. The metformin alone study arm showed a treatment failure of 51.7%. The metformin with lifestyle modifications had a slightly lower failure rate of 46.6% that was not statistically significant compared to the metformin alone group. Despite this, however, these patients did reach their target weight loss at a higher rate compared to the metformin alone group and the metformin with rosiglitazone group. Metformin with rosiglitazone had the best outcome with a treatment failure of 38.6%.

Despite the fact that metformin with rosiglitazone showed the best outcome with the lowest treatment failure, rosiglitazone is not FDA approved for use in children and adolescents. This study does indicate however, that early combination therapy may be more effective in the pediatric population. Combination therapy may be with insulin or another oral glucose lowering agent in addition to metformin.

Deciding on whether to initially start metformin or insulin in patients with newly diagnosed Type 2 Diabetes Mellitus depends on the presentation of the patient. If the patient presents with ketosis or ketoacidosis, then insulin therapy is to be started first. If the diagnosis of type 2 or type 1 diabetes is unclear, insulin should be started initially as well. The dose of insulin to be started may be in the range of 0.75-1.25 units/kg/day. This amount may be titrated up to 2 units/kg/day. These patients should monitor their glucose levels with a glucometer 3-4 times a day. Once the patient is no longer in ketosis, metformin may be added and insulin weaned off until the patient no longer requires insulin.

In patients who are not in ketosis and clearly have Type 2 Diabetes Mellitus, metformin may initially be started at 500mg/day. This may be gradually increased by 500mg increments every week until a maximum daily dose of 2000mg is reached. Metformin should be given with meals to decrease GI distress that can be associated with the drug. One of the adverse effects of metformin is lactic acidosis and is therefore contraindicated in patients who have impaired renal function, hepatitis, cirrhosis, or cardiopulmonary insufficiency. Patients with these conditions should be put on insulin therapy instead.

The goal for children and adolescents with Type 2 Diabetes Mellitus should be very strict glycemic control with a HbA1c less than 7% and a fasting plasma glucose of less than 130. HbA1c levels should be checked every 3 months, and self-monitoring in patients who are not on insulin should be about 1-2 times a day. Therapy may be intensified depending on whether the patient is reaching their target goal. Those who are not well controlled with

metformin may be started on long-acting insulin.

Along with the appropriate treatment, these patients also need to be screened for comorbidities that need to be managed as well. The comorbidities that they need to be screened for include hypertension, dyslipidemia, nonalcoholic fatty liver disease, microvascular disease (retinopathy, nephropathy, and neuropathy), and CV disease. Secondary complications of diabetes may be present at the time of diagnosis in these patients as well.

Essential Hypertension is the most common cause of hypertension in adolescents. This is due to the rise in childhood obesity. Just as in adults, children with Type 2 Diabetes Mellitus and hypertension are at increased risk of vascular complications. Therefore, blood pressure should be measured at each visit. Once a patient with Type 2 Diabetes is diagnosed with HTN, pharmacological therapy should be started.

Along with hypertension these patients are also to be screened for dyslipidemia. After glycemic control is established, a fasting lipid panel should be obtained and repeated every 2 years if the results are normal. If the results are abnormal, lipid panels should be obtained more frequently. First line treatment for dyslipidemia in these patients is diet control and increased exercise activity. If after 6 months these patients continue to have elevated lipid levels, then a statin may be started. Complications of dyslipidemia in these patients include nonalcoholic steatosis which may lead to fibrosis and scarring. This can lead to cirrhosis if not treated properly. Metformin use in patients with NASH is contraindicated due to the risk of lactic acidosis. Therefore, these patients should also have their liver enzymes monitored as well.

Just as in adults, microvascular complications are also a risk for children and adolescents with Type 2 Diabetes Mellitus. The risk of complications increases with the duration of the disease and with the amount of poor glycemic control. Therefore, annual ophthalmologic screenings should be performed in these patients for diabetic retinopathy. Due to possible neurologic and renal complications secondary to microvascular disease, annual screenings for microalbuminuria and diabetic neuropathy should also be done.

In conclusion, with the high rate of obesity in children and adolescents, we are beginning to see Type 2 Diabetes Mellitus in this patient population more frequently than in the past. Because the poor management of an illness like this has dire consequences, it is important for physicians to take an aggressive approach to treating these patients. Lifestyle modification plays a vital role in the treatment of these patients and although that by itself is very complicated and difficult to manage, in children the situation is complicated further by the fact that the entire family needs to work together in order for the lifestyle modification to be sustainable and effective. Along with lifestyle modifications, pharmacological treatment is necessary and studies continue to be done in order to determine the most effective therapy for these patients that will minimize failure rates.

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GASTROINTESTINAL TRAUMA - REVIEW

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Introduction and Statistics

Trauma is the most common cause of death among individuals between 1 and 44 years old and the 3rd leading cause of death in all age groups [1]. Types of trauma include blunt trauma, penetrating trauma, burn injuries and barotrauma. Gastrointestinal (GI) trauma refers to injury to the stomach, small intestine, large bowel, and rectum.

Blunt trauma commonly involves motor vehicle accidents. Unintentional injury is the 5th leading cause of death with over 27% related to motor vehicle accident (MVA) [2]. In 2012, there were 5.6 million police reported motor vehicle accidents with over 2.3 million people injured and over 30,000 fatalities [3]. Penetrating trauma commonly involves gunshot wounds and stab wounds. In 2009, the U.S. population of 305.6 million had a total of 310 million firearms. Of fatal injuries, 19,392 involved suicide and 11,078 were homicides [4]. Of the 12,765 murder cases in the U.S., 12.5% involving knives and cutting instruments and about 70% involving firearms [5]. Burn injuries requiring medical treatment was 450,000 from 2002-2011. The yearly fire and burn deaths per year were 3,400 with a survival rate of 96.1%. Most burn injury (69%) occurred in the home [6].

Solid organ injury (e.g. liver, spleen, or kidneys) is more common than hollow viscus injury. GI injury can be due to blunt mechanisms (motor vehicle crash, pedestrian injury, or falls) or penetrating mechanisms (knife, gunshot wounds). Most blunt GI injures are due to motor vehicle crashes [2]. However, GI injury in blunt trauma is uncommon. Of the over 220,000 admissions for blunt trauma in the EAST Multi-Institutional Trial, less than 1% of patients had injury to the GI tract. However, mortality in patients with any form of hollow viscus injury was higher than patients without GI injury [7].

Initial Assessment

Management of trauma is based on protocols from the Advanced Trauma Life Support (ATLS), established by the American College of Surgeons Committee on Trauma. Initial Assessment includes the primary survey with concurrent resuscitation/treatment, and the secondary survey. The primary survey includes management of airway including cervical spine protection, breathing, and circulation (ABCs). All patients with blunt trauma should be assumed to have an unstable cervical spine until proven otherwise [8]. The primary survey is done quickly to address the most life-threatening conditions and is concurrent with resuscitation and treatment. Injuries that should be immediately identified and addressed during the primary survey include airway obstruction, tension pneumothorax, massive internal and external hemorrhage, open pneumothorax, flail chest, and cardiac tamponade. The ABCs are followed by a brief neurological examination for disability and complete disrobing of the patient to examine for occult bruising, lacerations, impaled foreign bodies and open fractures. The primary survey is followed by the secondary survey, which is a more thorough head-to-toe examination while resuscitation continues [9].

The novel concept to damage control resuscitation (DCR) addresses the lethal triad of hypothermia, acidosis,

and coagulopathy. DCR combined with damage control surgery/laparatomy (discussed below) has been shown to improve 30-day survival in trauma patients [10]. The concept focuses on body rewarming, reversing acidosis, permissive hypotension, restricting fluid administration and hemostatic resuscitation. Reversal of acidosis is better achieved with blood and blood products and vasopressors than with use of bicarbonate or tris-hydroxymethal aminomethane (THAM). Permissive hypotension is the idea of limiting fluids and/or blood products and targeting a lower than normal blood pressure of 80-90 systolic or a mean arterial pressure of 50 mmHg. It has also been shown that aggressive fluid resuscitation worsens coagulopathy, increases the incidence of acute respiratory distress syndrome, pulmonary edema, compartment syndrome, anemia, thrombocytopenia, pneumonia, electrolyte abnormalities and overall increases mortality. Finally, the DCR strategy aims at early and aggressive administration of blood and blood products, specifically at a ratio of packed red blood cells, fresh frozen plasma, and platelets of about 1:1:1 [10]. These approaches have been shown to improve survival.

Mechanism of Injury

GI injury in blunt trauma is usually due to crushing of abdominal organs between the spine or pelvis and an object of the vehicle, e.g. steering wheel, seatbelt, or handle bar of a motorcycle. GI injury most commonly involves the small bowel (jejunum/ileum), followed by colon/rectum, duodenum, stomach and appendix [7].

About 40% of individuals with blunt trauma have surgically important bowel and/or mesenteric injury [11]. Blunt small bowel injury can be difficult to detect because the injury may not be immediately present and intestinal rupture may take days to develop. In contrast, penetrating intestinal injury will result in immediate intestinal leakage.

Colon and rectal injuries are relatively uncommon [12]. Mesenteric injury in blunt trauma usually occurs at points where the colon is fixed to the retroperitoneum, e.g. at the ileocecal valve and sigmoid colon. The retroperitoneal location of the colon makes diagnosis of colon injury difficult. Pelvic fractures may be associated with injury to the rectum [13].

Injury to specific organs in penetrating trauma depends on the type of object, the location of the injury, and the velocity of the object. The high energy of bullets makes multiple injuries more likely with gunshot wounds than with stab wounds.

History and Physical

The trauma history should assess the risk for GI injury. Abdominal pain is not specific for GI injury. Physical examination findings may include abdominal wall ecchymosis, abdominal distention and tenderness, or signs of peritoneal irritation. These signs are also not specific for GI injury. However, lack of abdominal pain or tenderness decreases the likelihood of finding a GI injury that would require surgery. The same senior level physician should do serial physical exams over at least 16 to 24 hours to avoid missing injury from blunt trauma [14].

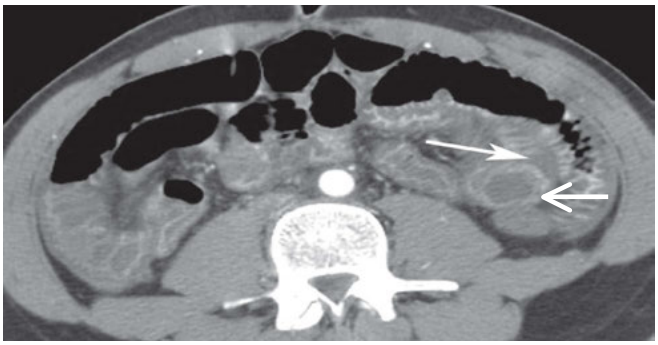
Diagnostic Evaluation

The Focused Assessment with Sonography for Trauma (FAST) serves as a screening tool to detect peritoneal bleeding in blunt abdominal trauma. Prospective studies have shown that the FAST exam has sensitivity from 69-90% and specificity of 95-100% in detecting free intraperitoneal fluid [15]. The role of the FAST exam in penetrating trauma is more limited. However, it can be used to plan surgical intervention in patients with multiple wounds [15]. A negative FAST exam should be followed by other tests, e.g. computed tomography (CT), diagnostic peritoneal lavage (DPL), or with laparotomy in unstable trauma patients.

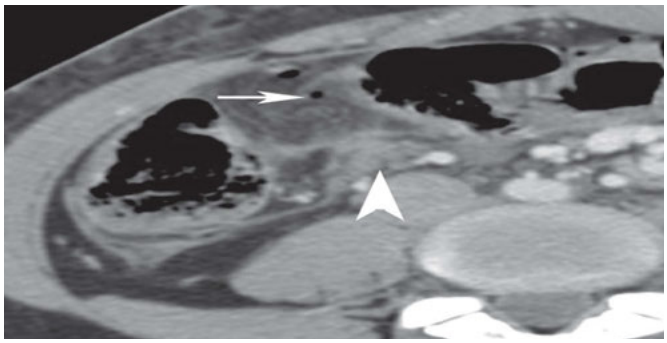
Although DPL is rarely needed now with the introduction of FAST and improvements in CT, it can be used as an adjunct in more stable patients. The fluid can be assessed for a red blood cell count (RBC), white blood cell count (WBC), and amylase. A positive test indicates the need for abdominal exploration [16].

CT of the abdomen is the most sensitive imaging test for identifying GI injury in stable patients with blunt trauma [17]. The role of CT in penetrating injury is less well-defined. CT scan findings in traumatic GI injury include pneumoperitoneum, mesenteric air, discontinuity in the wall of hollow viscus, intra-abdominal fluid without solid organ injury, extravasated intravenous contrast, bowel wall thickening or edema, mesenteric hematoma, hemoperitoneum or hemothorax and dislocated organs or bones [17]. (See images).

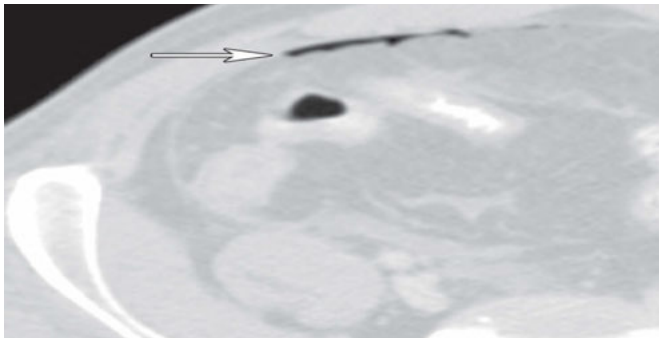
In a review of multidetector CT scan (MDCT) used after abdominal blunt trauma, sensitivity ranged from 70-95%



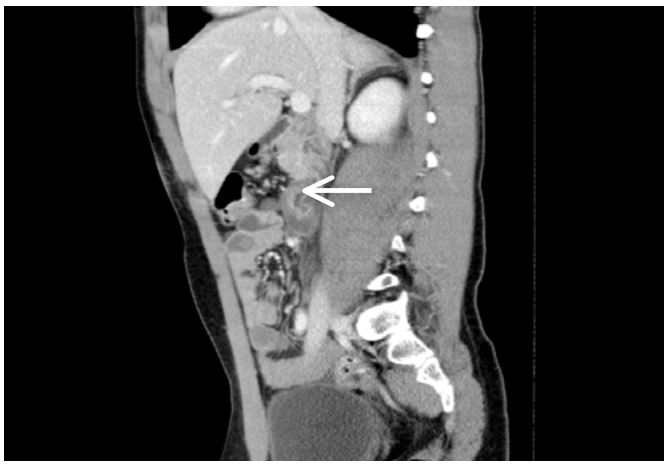
Bowel Wall Thickening (arrow pointing left) with anterior fluid collection (arrow pointing right) from ileal perforation



Peritoneal Air Bubble (arrow), mesenteric hematoma (arrowhead)



Intra-Peritoneal Air



Duodenal Hematoma (arrow = thickened duodenum)

and specificity ranged from 92-100% for the diagnosis of bowel and mesenteric injuries [18].

Definitive care

Hemodynamically unstable trauma patients should be transferred immediately to the operating room for evaluation and management [8]. Abdominal exploration allows for control of mesenteric bleeding, evaluation of bowel viability, and management of intestinal injuries. Options for intestinal repair include the one-layer hand-sewn technique, the two-layer hand-sewn technique, or stapled technique. Hand-sewn and stapled techniques have been shown to have similar complication rates, e.g. anastomotic leak and/or infection in elective surgery. However, in trauma patients, use of stapled techniques for GI anastomoses showed in increase incidence of postoperative complications, e.g. anastomotic dehiscence and formation of intra-abdominal abscess [19].

Repair may be based on the American Association for the Surgery of Trauma (AAST) Injury Scoring Scale for specific organs [20]. See Injury Grading table on next page.

Repair of grade I partial-thickness lacerations should be by primary repair in one or two layers. Intramural hematomas should be opened and evacuated. Grade II laceration injuries should be repaired with debridement to fresh margin. Debridement and primary closure can be used for grade III and many larger lacerations of the small bowel, colon, and rectum. A gastric laceration near the pylorus should be repaired transversely to preserve a wide gastric outlet. An injury at the gastroesophageal junction should be repaired over a nasogastric tube with suction and possible fundoplication for support over the repair site. Grade IV and V injuries of the small or large bowel require resection and anastomosis [20].

Colorectal injuries requiring resection can subsequently involve primary anastomosis or use of colostomy. In a comparison between primary repair or primary anastomosis with resection versus colostomy with resection, the former did better in the majority of colorectal injuries [21]. Comorbid conditions, blood transfusion of > 6 units, shock, delayed operation, and fecal contamination were previously thought to increase the risk of complications following colon repair. However, research by the AAST found that abdominal complications are not influenced by the surgical method of repair, regardless of associated risk factors [21].

Injury Grading

Grade	*Stomach*	*Small Intestine and Colon*	*Rectum and Rectosigmoid Colon*
I	Intramural hematoma < 3cm, partial thickness laceration	Contusion or hematoma without devascularization; partial thickness laceration	Contusion or hematoma; partial thickness laceration
II	Intramural hematoma > 3cm, full thickness laceration < 3cm	Full thickness < 50% of circumference	Full thickness laceration < 50% of circumference
III	Full thickness laceration ≥ 3cm	Full thickness ≥ 50% of circumference	Full thickness laceration ≥ 50% of circumference
IV	Full thickness laceration involving vessels on greater and/or lesser curvature	Transection	Full thickness laceration with perianal extension
V	Extensive rupture > 50%; devascularization	Transection with segmental tissue loss; devascularized segment	Devascularized segment

Damage control laparotomy (DCL) is used in cases where the patient is unstable with the lethal triad of coagulopathy, acidosis, and hypothermia. In this approach, the initial surgery intervention is abbreviated with the goal of only hemorrhage and contamination control. DCL is followed by temporary abdominal closure in cases where there is heavy intra-abdominal contamination, risk of anastomotic breakdown, need for a second look operation, need to assess delayed bowel viability, and when there is risk for abdominal compartment syndrome. Definitive repair is done after normal physiology is restored, usually after 24 hours [22]. Drains are generally not preferred following repair or resection of most GI injuries. However, drains should be used prophylactically at the repair site in total gastrectomy with esophageal-jejunal anastomosis. Anastomotic leak is associated with a high mortality rate in this type of repair [23]. Postoperative care of trauma patients should be in the Intensive Care Unit with monitoring of intra-abdominal pressure.

Complications

The incidence of complications is between 22-29% [21]. Complications include pneumonia, sepsis, renal dysfunction, thromboembolism, surgical site infection, and intra-abdominal abscess. Patients with colon/rectum injuries have the highest complication rates. Overall mortality in patients with hollow viscus injury is 20%. The highest mortality is associated with patients with injury to the stomach [7].

Conclusion

GI injury involves injury of the stomach, small bowel, colon, or rectum. They are less common than solid organ injury and are more associated with penetrating trauma rather than blunt trauma. Although GI injury is uncommon in blunt trauma, it is associated with a high mortality rate. Physical examination is important in the evaluation of trauma patients. If the patient is hemodynamically stable, CT should be used to identify abdominal injuries. A DPL may be useful if CT scan is equivocal. Ultimately, abdominal exploration is required to establish the diagnosis. Abdominal trauma in a hemodynamically unstable patient requires open abdominal exploration. Using DCR and DPL is associated with improved mortality. If the patient is hemodynamically stable without peritonitis, imaging is indeterminate, and physical exam is reliable, observation may be appropriate.

The AAST grading system for GI injuries based upon CT or findings in the operating room is a useful tool. Bowel injury with severe associated injuries may require a damage control approach with delay of final repair up to 24 hours. Grade I, II and III GI injuries can usually be repaired primarily whereas resection is usually needed in cases with multiple injuries along the same segment or higher-grade injuries (Grade IV and V).

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MARIJUANA: HARMFUL DRUG OR BENEFICIAL MEDICINE?

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This article is dedicated to the life of the late Albert Ridlovsky, MD (August 1963 – March 2014), who practiced Internal and Addiction Medicine in Southern California. He specialized in Opioid Dependency, Alcoholism, Substance Abuse, and Pain Management.

Abstract:

The use of marijuana as medicine has advanced in the past decade as 18 states now feature laws that legalize its use for medical purposes. Cannabis, or marijuana, has been used for medicinal purposes for many years. Several types of cannabinoid medicines are available in the United States and Canada. Dronabinol (schedule III), nabilone (schedule II), and nabiximols (not US Food and Drug Administration approved) are cannabis-derived pharmaceuticals. This article will describe the pharmacology of cannabis and the uses and abuses of cannabis, will discuss whether it is a beneficial or harmful drug, and will chart the current legislative status of medical marijuana across the US.

Introduction

The case for whether medical marijuana (Cannabis sativa used to treat a wide variety of pathologic states) should be legalized as a legitimate pharmaceutical agenda is complicated. Possible benefits need to weighted against increased risks such as cancer, pulmonary problems, damage to the immune system, negative psychological effect. This article will describe the pharmacology of cannabis and the uses and abuses of cannabis plus discuss whether it is a beneficial or harmful drug, and chart the current legislative status of medical marijuana across the United States.

Physical Properties

The physical properties of marijuana produce a variety of active substances from six known unique compounds, all called cannabinoids. The most active is Trans-Delta-9 Tetrahydrocannabinol (THC). THC is intensely lipophilic and may bind non-specifically to a variety of receptors in the brain and body such as adipose tissue.[1] The acute effects of cannabis depend upon the concentration. The effects are determined by past experience, and added to by the expectations and ego strength of the user. It is more effective on adolescents and less effective on adults. Adolescents known to have unstable personalities or to suffer from personality problems, particularly serious affective disorders or permanent psychosis, may experience enhanced symptoms with marijuana use.

Pharmacokinetics

Absorption Types

Smoking cannabis results in more rapid onset of drug action (within minutes), higher blood levels of cannabinoids, and a shorter duration of pharmacodynamic effects compared to oral administration.[2] The vaporization of cannabis has been explored as an alternative to smoking, with the potential advantages being the formation of a smaller quantity of byproducts such as carbon monoxide and tar.[3] Oral administration results in a slower onset of drug action, lower peak blood levels of cannabinoids, and a longer duration of pharmacodynamic effects compared to smoking.[2] When administered oromucosally, peak plasma concentrations typically occur within 2 to 4 hours, although there is wide interindividual variation in the peak cannabinoid plasma concentrations and in the time of onset and peak of effects.[4] Cannabinoids are highly hydrophobic, making transport across the

aqueous layer of the skin the rate-limiting step in the diffusion process. No clinical studies exist regarding the percutaneous absorption of cannabis-containing ointments, creams or lotions.[2]

Distribution

Distribution begins immediately after absorption and is taken up primarily by fatty tissues and organs such as the brain, heart, lungs and liver. Highest concentrations are found in the heart and adipose tissue with accumulation and retention of cannabis in the fatty tissue. Its release from the fatty tissue into the blood is slow.[5] Pharmacokinetic excretion of marijuana occurs via the feces (65%) and the urine (20%). After five days, 80 to 90% of the total dose is excreted.[6]

Marijuana Use versus Abuse

Recreational Marijuana

Marijuana is the most commonly used illicit drug (17.4 million past-month users) according to the 2010 National Survey on Drug Use and Health (NSDUH). That year, marijuana was used by 76.8% of current illicit drug users (defined as having used the drug at some time in the 30 days before the survey) and was the only drug used by 60.1% of them.[7]

The primary mode of using marijuana is inhaling the smoke of cigarettes, called joints. One joint contains approximately 500 to 750mg of marijuana, which is wrapped in thin paper, lit, and the smoke then inhaled.

In the youthful daily marijuana smoker, marijuana use often progresses in a predictable step-like fashion with consecutive doses escalating higher and higher. If individuals use marijuana during their early adolescence, they are likely to move on to other illicit drugs, such as cocaine or other hallucinogens, as marijuana has been demonstrated to be a gateway drug, facilitating abuse to higher levels or use/abuse of other drugs.[8]

Medical Marijuana

Despite legal restrictions in most states, marijuana is often used to relieve chronic and neuropathic pain, as well as cancer pain. Medicinal use of cannabis is often underreported,[9] as pain and muscle spasms are the most common symptoms for which medical marijuana is recommended. Several types of cannabinoid medicines are available in the United States and Canada, including dronabinol (schedule III), nabilone (schedule II) and nabiximols (not US Food and Drug Administration, FDA, approved), which are cannabis-derived pharmaceuticals.

The FDA has also approved Marinol® – a low-dosage formulation of synthetic THC that comes in capsule form. The drug is used to stimulate appetite in people with human immunodeficiency virus (HIV), as well as to control nausea and vomiting associated with chemotherapy. This presents an option for people with conditions such as cancer, which do not respond to common drugs. Marinol® also lowers intraocular pressure for glaucoma patients and is known to reduce anxiety.[8]

Marinol® is only one of two FDA-approved THC-based drugs. An issue with Marinol®, compared with Advil®, is that the body does not absorb it well. Only approximately 10 to 20% of the dose becomes available for the body to use, making it highly unpredictable. Marinol® is effective for some patients, while others determine no benefit whatsoever.

Dronabinol and nabilone are also used for the treatment of nausea and vomiting associated with cancer chemotherapy and for weight loss associated with patients suffering acquired immune deficiency syndrome (AIDS).

Arguments Supporting Marijuana as a Beneficial Medicine

More than 100 controlled clinical trials of cannabinoids or whole plant preparation for various indications have been conducted since 1975. Patients receiving cannabinoids (both smoked marijuana and marijuana pills) showed improved immune function compared with patients receiving placebo, and also gained approximately 4 pounds more on average than patients receiving placebo. The findings of these trials have led to the approval of cannabis-derived medicines, including dronabinol, nabilone and a cannabis extract (THC/CBD 1:1), in several countries.[10]

As a result of the California State Legislature Medical Marijuana Research Act (SB847), the Center for Medicinal Cannabis Research (CMCR) has successfully conducted the first clinical trials of smoking cannabis in the US, for more than 20 years. Due to this program of systematic research, there is now reasonable evidence to suggest that cannabis is a promising treatment in selected pain syndromes caused by injury or diseases of the nervous

system, and may be a possible treatment for painful muscle spasticity associated with multiple sclerosis (MS). A clinical study of 30 adult patients with MS, conducted at the University of California (San Diego School of Medicine), has demonstrated that smoking cannabis may be an effective treatment for spasticity – a common and disabling symptom associated with this neurological disease.[11]

While further research is necessary to elucidate the mechanisms of action and discover the full therapeutic potential of cannabinoid compounds, the knowledge and new findings from the CMCR provide strong scientif ic evidence supporting medicinal use, which policy makers and the public can discuss to determine placement in medical care.

Arguments Supporting Marijuana as a Harmful Drug

The adverse psychological effects of marijuana use may include psychosis, panic attacks, flat affect, and lethargy the day after use, hence the term amotivational syndrome; there can be confusion, disorientation, delusion, and hallucinations associated with this condition.The chronic effects of cannabis are developmental of amotivational syndrome, as highlighted by loss of interest, general apathy, passivity, loss of desire to work, lack of productivity, increased tiredness, loss of energy, increased frustration, poor concentration, and decrease in lifestyle.Adolescents in particular may also experience changes in mood, including depression and irritability, and may easily be provoked.[7]

Marijuana's negative effects on coordination and reaction time have been documented. Safe operation of vehicles is often compromised if a driver is acutely intoxicated, as marijuana can impair motor function in ways such as slower reflex time.There can be problems with oversensitivity to sensory stimuli, while spatial coordination and distance navigation are also impaired. In addition, marijuana-intoxicated drivers may fail to respond to visual cues due to preoccupation with music or a drug-induced euphoric state, which can last up to 24 hours.[7]

Marijuana can also have physiological effects on the lungs, heart, eyes, and brain. Pulmonary effects can include impairment of airway conduction, especially in asthmatics.Atrial fibrillation is a cardiovascular complication of marijuana smoking and physicians should be aware of this particular condition in order to treat patients with marijuana-related palpitations, dizziness or fainting. Furthermore, if a young patient without predisposing factors develops atrial fibrillation, the possibility of marijuana smoking should be considered as a potential cause.[7]

Legislation Status

The following chart documents the progress and position of legislation in regard to the legality of medical marijuana. Currently, 18 states and Washington, DC have enacted laws to legalize medical marijuana, the first law having been passed in California in 1996.

States Having Approved Medical Marijuana

Summary Chart: 18 States and DC have enacted laws to legalize medical marijuana

State	Year Passed	How Passed (Yes Vote)	Fee	Possession Limit	Accepts other states' registry ID cards?
1. Alaska	1998	Ballot Measure 8 (58%)	$25/$20	1 oz usable; 6 plants (3 mature, 3 immature)	unknown
2. Arizona	2010	Proposition 203 (50.13%)	$150/$75	2.5 oz usable; 0-12 plants	Yes3
3. California	1996	Proposition 215 (56%)	$66/$33	8 oz usable; 6 mature or 12 immature plants	No
4. Colorado	2000	Ballot Amendment 20 (54%)	$35	2 oz usable; 6 plants (3 mature, 3 immature)	No
5. Connecticut	2012	House Bill 5389 (96-51 House, 21-13 Senate)	Commissioner will establish a reasonable fee.	One-month supply (exact amount to be determined)	No
6. DC	2010	Amendment Act B18-622 (13-0 vote)	$100/$25	2 oz dried; limits on other forms to be determined	No
7. Delaware	2011	Senate Bill 17 (27-14 House, 17-4 Senate)	$125	6 oz usable	Yes
8. Hawaii	2000	Senate Bill 862 (32-18 House; 13-12 Senate)	$25	3 oz usable; 7 plants (3 mature, 4 immature)	No
9. Maine	1999	Ballot Question 2 (61%)	No fee	2.5 oz usable; 6 plants	Yes
10. Massachusetts	2012	Ballot Question 3 (63%)	TBD7	Sixty day supply for personal medical use	unknown
11. Michigan	2008	Proposal 1 (63%)	$100/$25	2.5 oz usable; 12 plants	Yes
12. Montana	2004	Initiative 148 (62%)	$25/$10	1 oz usable; 4 plants (mature); 12 seedlings	No
13. Nevada	2000	Ballot Question 9 (65%)	$2,008	1 oz usable; 7 plants (3 mature, 4 immature)	Yes
14. New Jersey	2010	Senate Bill 119 (48-14 House; 25-13 Senate)	$200/$20	2 oz usable	No
15. New Mexico	2007	Senate Bill 523 (36-31 House; 32-3 Senate)	$0	6 oz usable; 16 plants (4 mature, 12 immature)	No
16. Oregon	1998	Ballot Measure 67 (55%)	$200/$10010	24 oz usable; 24 plants (6 mature, 18 immature)	No
17. Rhode Island	2006	Senate Bill 0710 (52-10 House; 33-1 Senate)	$75/$10	2.5 oz usable; 12 plants	Yes
18. Vermont	2004	Senate Bill 76 (22-7) HB 645 (82-59)	$50	2 oz usable; 9 plants (2 mature, 7 immature)	No
19. Washington	1998	Initiative 692 (59%)	NA	24 oz usable; 15 plants	No

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ProCon.org."20 Legal Medical Marijuana States and DC" ProCon.org. 03 Oct. 2013

http://medicalmarijuana.procon.org/view.resource.php?resourceID=000881#

Currently, six states have pending legislation to legalize medical marijuana as of June 7, 2013.The chart below documents which states and what bills are being considered.

States with Pending Legislation to Legalize Medical Marijuana

Six States with Pending Legislation to Legalize Medical Marijuana as of June 7, 2013		
State	**Bill**	**Bill Summary**
1. Illinois	House Bill 1	Compassionate Use of Medical Cannabis Pilot Program Act: "AN ACT concerning alternative treatment for serious diseases causing chronic pain and debilitating conditions.
	House Bill 1076	Creates the Compassionate Use of Medical Cannabis Pilot Program Act. Contains only a short title provision and a section on findings. Makes findings on the medical use of cannabis to treat medical conditions.
2. Minnesota	Senate Bill 1641	Permitting the medical use of marijuana... specifying certain limitations... [establishing] registry identification card... authorizing cities to enact zoning regulations that limit use of land for medical marijuana dispensaries.
	House Bill 1818	Marijuana medical use permitted, fees set, rulemaking authorized, criminal and civil penalties provided, and money appropriated.
3. New Hampshire	House Bill 573	AN ACT relative to the use of marijuana for medicinal purposes... This bill permits the use of marijuana for medicinal purposes in New Hampshire.
4. New York	Senate Bill 1682	Legalizes the possession, manufacture, sale, administration, delivery, dispensing and distribution of [up to 8 oz of] marijuana in connection with medical use thereof for certified patients... permits registered organizations to sell, administer, deliver, etc. marijuana to certified patients or the caregiver of a certified patient for certified medical use.
	Senate Bill 4406	Legalizes the possession, acquisition, use, delivery, transfer, transport or administration of marihuana by a certified patient or designated caregiver for a certified medical use
5. Ohio	Assembly Bill AB6357	Legalizes the possession, acquisition, use, delivery, transfer, transport or administration of marihuana by a certified patient or designated caregiver for a certified medical use
	House Bill 153	A registered primary caregiver: A registered qualifying patient or visiting qualifying patient for engaging in the medical use of cannabis;... A registered primary caregiver.
6. Pennsylvania	Senate Bill 770	An Act providing for the medical use of marijuana; and repealing provisions of law that prohibit and penalize marijuana use.
	House Bill 1181	An Act providing for the medical use of marijuana.

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Four states have passed legislation that leans favorably toward the use of medical marijuana but does not legalize it. As a physician, it is important to know where your state stands in the medical marijuana legal debate.

States Favorable Toward Medical Marijuana but Would Not Legalize Its Use

States with 2013 Legislation That Is Favorable Towards Medical Marijuana But Would Not Legalize Its Use		
State	**Bill**	**Summary**
1. Maryland	House Bill 180	Medical Marijuana Caregiver Affirmative Defense: "Establishing that it is an affirmative defense to a prosecution for the possession of marijuana or the possession of specified drug paraphernalia that the marijuana or drug paraphernalia was intended for medical use by an individual with a specified debilitating medical condition for whom the defendant is a specified caregiver.
	House Bill 1101	This bill allows for the investigational use of marijuana for medical purposes. Specifically, the bill establishes the Medical Marijuana Commission to (1) develop requests for applications for academic medical centers to operate programs in the State; (2) approve or deny initial and renewal program applications; and (3) monitor and oversee programs approved for operation."
2. Minnesota	House File 508	Courts authorized to recognize a necessity defense for criminal, administrative, and civil cases involving natural herbs of the genus Cannabis.
3. Oklahoma	Senate Bill 902	Legalizes the possession, manufacture, sale, administration, delivery, dispensing and distribution of [up to 8 oz of] marijuana in connection with medical use thereof for certified patients... permits registered organizations to sell, administer, deliver, etc. marijuana to certified patients or the caregiver of a certified patient for certified medical use.
4. Texas	House Bill 594	An Act relating to the medical use of marihuana: It is an affirmative defense to prosecution... that the person possessed the marihuana as a patient of a physician licensed to practice medicine in this state pursuant to the recommendation of that physician for the amelioration of the symptoms or effects of a bona fide medical condition.

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Currently, 12 states have defeated legislation to legalize medical marijuana, predominantly from the Southern and Midwestern states.

States with Failed Legislation

States with Failed Legislation	
State	**Bill**
1. Alabama	House Bill 2
	House Bill 315
2. Iowa	Senate File 79
	House File 22
3. Florida	Senate Bill 250
	House Bill 1139
4. Kansas	Senate Bill 9
	House Bill 2198
5. Kentucky	Senate Bill 11
6. Maryland	House Bill 302
	House BIll 1100
7. Mississippi	Senate Bill 2369
8. Missouri	House Bill 688
9. North Carolina	House Bill 84
10. Oklahoma	Senate Bill 710
11. South Dakota	House Bill 1227
12. West Virginia	House Bill 2230
	House Bill 2961

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Conclusion

All major medical organizations support the FDA approval process. In its policy statement, the American Medical Association (AMA) recommends that for now, marijuana remain classified as a Schedule I Controlled Substance. This classification means that marijuana has a high potential for abuse, unaccepted medical use and a lack of acceptable safety. However, this is transposed with the AMA recommending to the National Institutes of Health (NIH) for more studies on the drug, urging the NIH "to implement administrative procedures to facilitate grant applications and the conduct of well-designed clinical research into the medical utility of marijuana."[12]

In its 2011 policy statement, the American Osteopathic Association (AOA) "…supports well-controlled clinical studies on the use of marijuana and related cannabinoids for patients who have significant medical conditions for which current evidence suggests possible efficacy; and encourages the National Institutes of Health (NIH) to facilitate the development of well-designed clinical research studies into the medical use of marijuana." [13]

The American College of Osteopathic Family Physicians (ACOFP), in their paper, "The Role of the Physician in

"Medical Marijuana", concludes that all cannabis-based and cannabinoid medication should be subjected to the rigorous scrutiny of the FDA regulatory process.

This process provides important protections for patients, making medications available only when they: 1) are standardized by identity, purity, potency, and quality; 2) are accompanied by adequate directions for use in the approved medical indication; and 3) have risk/benefit profiles that have been defined in well-controlled clinical trials. [14]

Discussion amongst policy makers and within the public regarding the medicinal use of marijuana needs to address that there is a significant need for FDA trials before a drug is used in society, As long as the possibility of medical use exists, a need for testing also exists.

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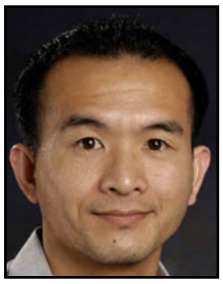
APOLIPOPROTEIN E DOWNREGULATES THE PRODUCTION OF IL-1 IN INDIVIDUALS WITH HIV INFECTION



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Introduction

More than 40 million people have died so far because of acquired immunodeficiency syndrome (AIDS) caused by human immunodeficiency virus (HIV) (13). Currently 34 million people around the world are infected with HIV. And every year, an additional 2.7 million individuals are getting infected with HIV (13). Roughly 23 of the 34 million people who are infected with HIV live in sub-Saharan Africa where Mycobacterium tuberculosis (M. tb) is endemic (13). According to Bloom and Murray reported in 1992, tuberculosis (TB) is the most prevalent infectious disease in the world. While M. tb infection in HIV positive individuals is a worldwide epidemic (1). In many developing countries, as many as 80% of HIV infected individuals are also co-infected with M. tb (8) and this susceptibility for the opportunistic infection is a reason for increased incidence of mortality.

Previously, we reported that M. tb is sensitive to the intracellular antioxidant, glutathione (GSH) which is an important tripeptide molecule that is involved in the balance of redox reactions and helps in maintenance of cellular homeostasis and protein transport (3). In its reduced form, GSH protects the body against free radicals, oxidizing agent, and reactive oxygen species (ROS) (7). HIV infected individuals are immunocompromised and, from our previous studies, we know that the levels of GSH are compromised in individuals with HIV infection and this decrease correlated with increased production of free radicals (4, 5, 9, 10, 11, 12). This redox imbalance leads to cellular stress and impairment of host defense.

IL-1, a pro-inflammatory cytokine plays an important role in the host innate immune response. IL-1 is mainly produced by the macrophages and is responsible for regulating the function of immune cells. While optimal production of IL-1 is extremely beneficial for controlling infections, excessive production can result in an inflammatory response. Interestingly, individuals who are infected with HIV mount ineffective immune responses due to deficiency in CD4 T cells resulting in decreased production of cytokines such as IL-12 and IFN- (6). In HIV-infected individuals, IL-1 production is lower compared to healthy individuals.

Apolipoprotein (ApoE) is a 34-kDa lipoprotein that has many biological implications such as lipid metabolism, cardiovascular diseases, and neurodegenerative disorders such as Alzheimer's disease (AD) and Parkinson disease (PD). Apo E has also been shown to have immunomodulatory properties (14). Synthesis of this protein is influenced by lipid levels, production of nitric oxide (NO) and IL-1 (14). Several in vivo studies that were performed in animal models have reported

that inactivation of Apo E gene increased levels of GSH (2, 10). In our study on a HIV-infected individual, we demonstrate that increased levels of Apo E can down regulate the levels of GSH and IL-1. Furthermore, we show restoration in the levels of IL-1 after the HIV-infected individual received an oral GSH-supplement formulated in liposomes (L-GSH).

Case Report

Our participant is a 29-year old HIV positive Caucasian male, first diagnosed with HIV infection in 2011. Patient voluntarily participated in our L-GSH supplementation study. The patient was asked to take 1 1/2 teaspoons of L-GSH twice a day for 13 weeks. L-GSH (ReadiSorb) was supplied by Your Energy Systems LLC (Palo Alto). The study was approved by the Institutional Review Board and Institution bio-safety committee of the Western University of Health Sciences. Patient completed the study and was compliant. Levels of Apo E, GSH and IL-1, were measured before the start of the study (baseline time point) and after completion of the study (13-weeks). Levels of Apo E, GSH and IL-1 in the HIV positive individual at the baseline time point was compared to the values from a healthy subject (25 year-old Asian male). L-GSH was given only to the HIV positive participant.

Levels of GSH in the lymphocytes were measured spectrophotometrically using an assay kit from Arbor Assay. Levels of IL-1 in the plasma samples were measured using an assay kit from Ebioscience. Levels of Apo E in the plasma were determined using an assay kit from AssayPro.

CD4 T cell numbers and liver enzymes (LabCorp) were also measured in the HIV participant before and after L-GSH supplementation.

Patient was asymptomatic and had a normal physical examination. The results of hematologic and other routine laboratory tests were normal. Patient was first enrolled in the study on 10/23/2013. Prior to taking L-GSH supplement (baseline time point), his CD4 T cell counts were 509 cells/mm3. After completion of 13-weeks on L-GSH supplementation (on 1/27/14), his CD4 T cell counts were 647 cells/mm3. Liver enzymes on 10/23/2013 (baseline time point) were as follows: AST 22 U/L and ALT 20 U/L. At 13-weeks of L-GSH treatment (on 1/27/2014), the read out for the liver enzymes are: AST 23 U/L and ALT 17 U/L.

At the baseline time point, the patient had significantly low levels of antioxidant GSH and IL-1 compared to the healthy individual (Figure 1A). However, the levels of Apo E were higher in the individual with HIV infection (Figure 1A). After the patient received L-GSH supplementation for 13 weeks, the levels of GSH and IL-1 were significantly increased compared to the baseline time point (Figure 1B) ; and the increase in IL-1 and GSH corresponded with decrease in the levels of Apo E (Figure 1B).

Discussion

A chronic HIV infected Individual is likely to have compromised immune system due to CD4 T cell deficiency and that results in increased susceptibility to opportunistic infections. Our patient who is a chronic HIV infected individual had elevated levels of free radicals (data not shown), decreased levels of both GSH and IL-1 , and significantly elevated levels of Apo E compared to the healthy individual (Figure 1A). After the HIV positive patient was given L-GSH supplement, there was an observed decrease in free radicals while GSH

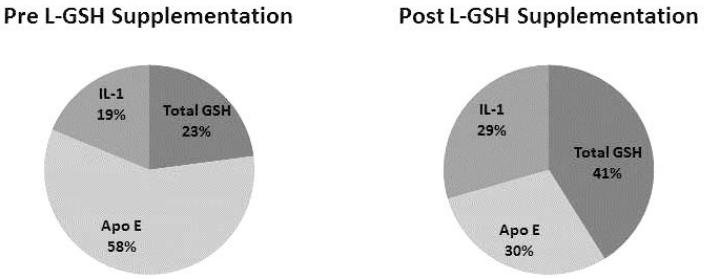

Figure 1B. Total GSH, IL-1, and Apo E levels in healthy individual and patient with HIV infected individual after L-GSH supplement for 13 weeks.

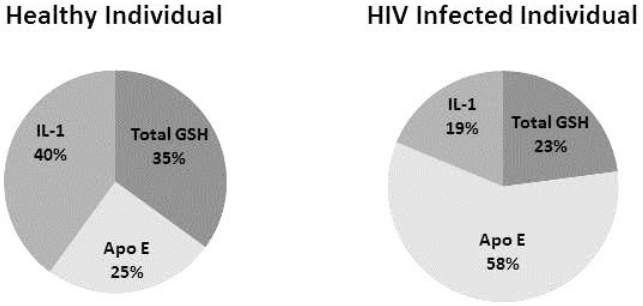

Figure 1A. Total GSH, IL-1, and Apo E levels in healthy individual and HIV infected individual

levels significantly increased (Figure 1B). We observed that L-GSH supplementation in the individual with HIV infection resulted in significant decrease in the levels of Apo E with concomitant increase in the production of n IL-1 (Figure 1B). This suggests that Apo E is implicated in down regulating the levels of both GSH and IL-1.

To conclude, Apo E plays an important role in altering the immune responses and regulating the production of IL-1. In addition to the antiretroviral treatment (HAART), other alternative therapy may provide promising and effective treatment and immunological benefits in individuals with HIV infection.

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RELAPSE OF LUPUS NEPHRITIS AFTER SUCCESSFUL REMISSION

A Case Study following National Treatment Guidelines

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Background

Systemic Lupus Erythematous (SLE) is an autoimmune disease that causes chronic inflammation of multiple organs including the skin, nervous system, kidneys, lungs, heart, joints and serous membranes. It primarily affects women in their second and third decades of life, with an incidence rate of 164 (Caucasians) to 460 (African Americans) per 100,0001. Of the patients afflicted with SLE, about 90% would show evidence of nephritic changes on kidney biopsy, with at least half of SLE patients presenting with clinically significant nephritic syndrome, a condition termed lupus nephritis2. Routine laboratory work indicating a sudden rise in serum creatinine or a urine dipstick showing proteinuria and/or hematuria should raise the suspicion for lupus nephritis. Symptoms associated with lupus nephritis are edema, weight gain, frothy urine, hematuria and nocturia.

Lupus Nephritis is ultimately diagnosed by obtaining a kidney biopsy in order to classify it as World Health Organization (WHO) class I-V, or as International Society of Nephrology (ISN)/Renal Pathology Society (RPS) class I-VI. The World Health Organization first published their Lupus Nephritis classification system in 1975 and revised it multiple times until 2001. In 2003 the ISN and RPS proposed a revision to this classification scheme that subdivided classes III and IV and added a sixth class representing advanced sclerosing Lupus Nephritis, which made the biopsy results easier to reproduce3. Class I-IV are on a spectrum of glomerulonephritis with a nephritic clinical presentation, as they are due to mesangial immune complex deposits that further invade the subepithelial and subendothelial spaces. Subclasses exist for Classes III and IV; they can be identified as active and/or chronic lesions. Active inflammation is called proliferative Lupus Nephritis, whereas chronic inflammation is called sclerosing Lupus Nephritis. Furthermore, Class IV is also classified by the degree of glomerulus involvement: if less than 50 percent of the glomerular tuft is affected it is termed segmental disease, whereas more than 50 percent involvement of the glomerular tuft is termed global disease. Thus, the letters "A", "C", "S" and "G" indicate active inflammation, chronic inflammation, segmental disease and global disease, respectively4,5. (Table 1)

Class V is a membranous nephritis, as the glomerular basement membrane is thickened, presenting as a nephrotic disorder. Class VI indicates an advanced stage with global sclerosis of most glomeruli. It is possible for Class V to co-exist with classes II-IV. Our clinical presentation is a case with combined characteristics of both nephritic and nephrotic syndromes as demonstrated by Figure 1. (Figure 1)

It is important to determine the class of lupus nephritis, as treatment guidelines differ for the individual classes.

Table 1: ISN/RPF Classification of Lupus Nephritis

Class		Biopsy
I	Minimal Mesangial Lupus Nephritis	Light Microscopy: Normal Immunofluorescence: Mesangial immune deposits
II	Mesangial Proliferative Lupus Nephritis	Light Microscopy: Purely mesangial hypercellularity or matrix expansion with mesangial immune deposits Immuofluorescence: Mesangial immune deposits and few isolated subepithelial or subendothelial deposits
III	Focal Lupus Nephritis	Light Microscopy: Active or Inactive focal, segmental or global endo- or extracapillary glomerulonephritis involving <50% of glomeruli Immunofluorescence: Focal subendothelial immune deposits, with or without mesangial deposits
IV	Diffuse Lupus Nephritis	Light Microscopy: Active or inactive diffuse, segmental or global endo- or extracapillary glomerulonephritis involving ≥50% of all glomeruli Immuofluorescene: Diffuse subendothelial immune deposits, with or without mesangial alterations.
V	Membranous Lupus Nephritis	Light microscopy: Diffuse thickening of basement membrane without inflammatory infiltrate. Immunofluorescence: Global or segmental subepithelial and intramembranous immune deposits. Shows advanced sclerosis.
VI	Advanced Sclerosing Lupus Nephritis	≥90% of glomeruli sclerosed without residual activity

For treatment of ISN/RPS class IV/V lupus nephritis, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest an induction therapy with corticosteroids plus either mycophenylate mofetil or cyclophosphamide until remission is achieved. Then, a maintenance therapy should follow induction that consists of corticosteroids (≤10mg/day prednisone equivalent) plus mycophenylate mofetil (1-2g/day in divided doses) or azathioprine (1.5-2.5 mg/kg/day). Once the patient achieves remission for 12 months, tapering of immunosuppressive medication can be considered. Furthermore, patients with ISN/RPS class V lupus nephritis should also be treated with antiproteinuric and antihypertensive medication to treat proteinuria and hypertension, respectively. To treat a relapse one should use the induction regimen that helped the patient enter remission initially. If this fails, a repeat kidney biopsy should be considered as the ISN/RPS class might have changed6.

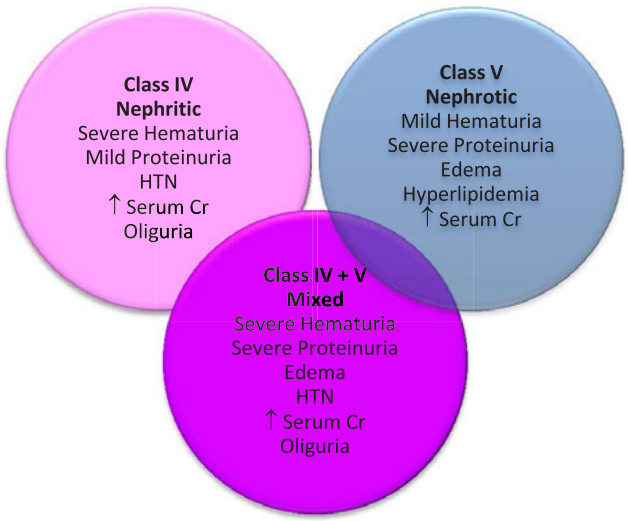

Figure 1: Comparing the findings of Nephritic syndrome (Class IV), Nephrotic syndrome (Class V) and its' possible coexistence (Class IV + V).

We defined remission of lupus nephritis as having had proteinuria <500mg per 24 hours for at least three months; however, there is no general consensus on its' definition. Furthermore, some studies use an inactive urine sediment as a criteria of remission7. Achieving complete remission is important as it improves renal survival rates. Unfortunately, a higher relapse rate is associated with a worse prognosis, and the current average relapse rate is 8 per 100 patient-years of follow-up8. Thus, it is important to prevent relapses of lupus nephritis.

Case Report

A 35-year-old Hispanic female with a past medical history of systemic lupus erythematous since 2007 presents to her rheumatologist with a malar rash, joint pain, a pleural effusion and recent frothy urine with increasing nocturia. This SLE flare was treated with prednisone 20mg per mouth once daily and mycophenolate mofetil 500mg per mouth once daily. However, urine dipstick continued to reveal the presence of 3+ protein. This was the first incidence of proteinuria for this patient. A 24-hour urine protein revealed 1867.3 mg per 24 hours upon which she was referred to a nephrologist for further evaluation.

During her nephrology evaluation, the patient confirmed the recent frothy urine as well as increasing nocturia, but she denied edema, hematuria, and dysuria. On physical exam the patient's blood pressure was 122/83

mmHg, pulse was 66 bpm, her respiratory rate was 16 and she had a temperature of 97.6 °F. The patient was 62 inches tall and weighed 193.1 pounds, with a Body-Mass-Index of 35.4. The patient's medication regimen included prednisone 20 mg once daily, mycophenolate mofetil 500 mg once daily and lisinopril 10 mg once daily. On follow-up with the nephrologist, her 24-hour urine protein level was still elevated, at 1753.5 mg. At this time her lisinopril dose was increased to 20 mg once daily, however, it could not be titrated any further due to hypotension.

Two months later her kidney biopsy showed segmental to global endocapillary proliferative lesions with small cellular and fibrocellular crescents (Figure 2) which is consistent with WHO class IV lupus nephritis. However, electron microscopic findings showed mesangial hypercellularity and glomerular basement thickening with numerous subepithelial deposits, indicating WHO class V Lupus Nephritis (Figure 3). Thus, the final diagnosis is a mixed WHO class IV and V lupus nephritis (Figure 2 and 3). Furthermore, the fluorescent antibodies stain showed positive for IgG, IgA, IgM, kappa, lambda, C3 and C1q. This combination of antibodies is also referred to as the "full house" which is the typical glomerular immunoglobulin pattern seen in lupus nephritis. (Figure 4).

Once the diagnosis of WHO class IV/V lupus nephritis was made, the patient's lisinopril was continued at 20mg once daily, prednisone was increased to 60mg daily then tapered down by 5mg every week until 10mg per day was reached. Mycophenylate mofetil was increased to 1mg three times daily by mouth, which is in accordance with the KDIGO guidelines for the induction of remission of Lupus nephritis class IV/V. During the treatment alteration, the patients' urine protein had reached 2457 mg per 24 hrs. Over the next several months the patient's urine protein levels were checked every 1-2 months. After ten months of induction therapy the patient entered remission. As Figure 3 depicts, the patient had a urine protein level <500mg per 24 hours for a total of about 6 months, with values of 88mg and 370 mg per 24 hours. At this point her treatment regimen was decreased to a maintenance dose of prednisone 10mg once daily by mouth and mycophenylate mofetil 1mg twice daily by mouth. However, one month after she was switched to her maintenance dose regimen, her proteinuria increased to 576mg per 24hrs. The decision was made to continue to monitor the patient's proteinuria, and consider a re-induction protocol if her urine protein exceeded >1,000mg per 24 hours.

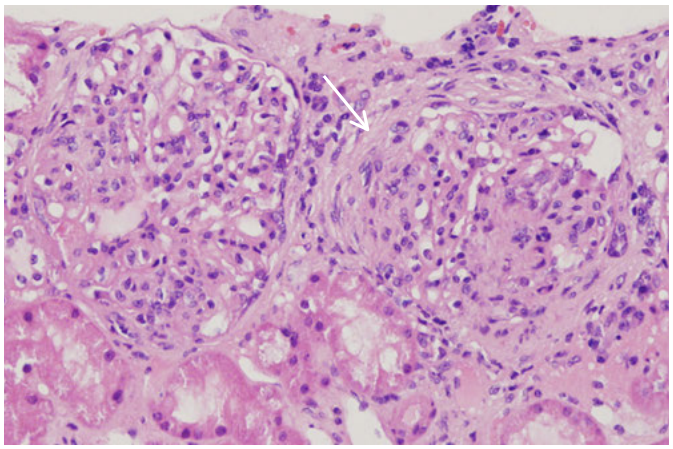

Figure 2: Light Microscopy showing a fibrocellular crescent, as indicated by the white arrow and segmental to global endocapillary proliferation. (With permission by Michael Koss, M.D. at the Pathology Department at the University of California, Los Angeles)

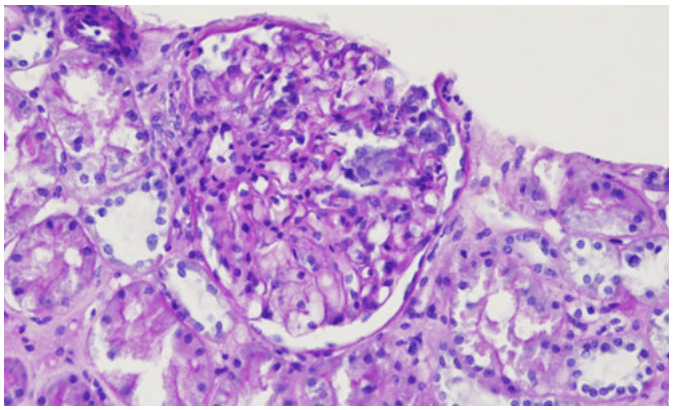

Figure 3: PAS stain highlighting mesangial hypercellularity and glomerular basement membrane thickening. (With permission by Michael Koss, M.D. at the Pathology Department at the University of California, Los Angeles)

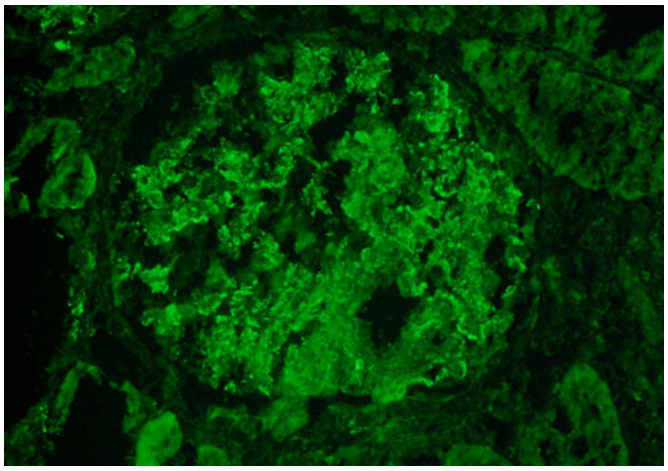

Figure 4: Immunofluorescent stain of IgM antibody on the glomerulus. In addition to IgM our patients' biopsy also stained positive for IgG, IgA, kappa, lambda, C3 and C1q. (With permission by Michael Koss, M.D. at the Pathology Department at the University of California, Los Angeles)

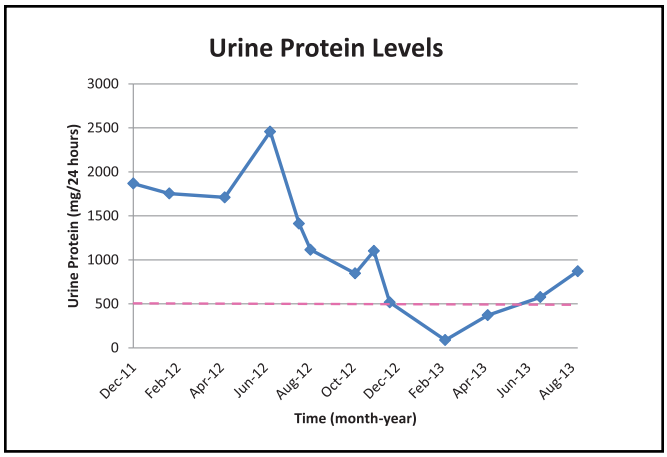

Figure 5:The blue line represents urine protein values in mg per 24 hours. Note the decrease after induction therapy initiation in July 2012.The pink dotted line represents our cut-off value for remission: 500mg/24hrs.

Discussion

This case illustrates that ISN/RPS class IV/V lupus nephritis relapses are a common complication. It is important to manage lupus nephritis until a complete remission is reached, since kidney failure is one of the major causes of death in SLE patients. A report from the Lupus Nephritis Collaborative Study Group stated that one can declare complete remission if creatinine clearance is ≤1.4mg/dL and urine protein is ≤330mg/day.7 We need a unified definition of remission of lupus nephritis in order to compare different researches on induction treatment modalities for lupus nephritis.

A similar challenge is encountered when defining Lupus nephritis relapse. Some studies define a relapse with urine protein of ≥330 mg or ≥2000 mg per 24 hours10. This makes it difficult for the nephrologist to decide when to re-start the original induction therapy, or when to stay at the maintenance therapy. In our case, our patient's urine protein values have exceeded 500mg per 24hrs. At this time it is arguable whether to restart the initial induction therapy or to wait for the proteinuria to reach higher values before making that decision. Relapse increases the risk of reaching end-stage renal disease 27 fold11.Therefore, aggressive and continuous therapy of lupus nephritis is essential. Further research is indicated to clarify the definitions of remission and relapse in these complex category of patients. It is also important to investigate further for better treatment regimens to ensure the complete remission of Lupus Nephritis.

The challenge in the primary care setting is to recognize SLE, as well as lupus nephritis. 16-32 percent of SLE patients present with nephritic disease at the time of SLE diagnosis12. If a previously healthy patient presents to the primary care physician with edema, nocturia, hematuria or frothy urine, following laboratory tests should be ordered including a complete blood count, serum creatinine, albumin, complement C3, antinuclear antibody levels, a Coomb's test and a complete urinalysis. Evidence of leukopenia, anemia, elevated serum creatinine, low albumin, low complement C3 levels, double-stranded DNA antibodies, Smith antigen and proteinuria should raise suspicion for Lupus Nephritis.The presence of proteinuria (>500mg per 24 hrs) and several of the fore mentioned laboratory results should warrant a referral to the nephrologist, as well as a rheumatologist to initiate an evaluation of lupus nephritis, and SLE, respectively.

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INPATIENT GLYCEMIC MANAGEMENT

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Introduction: The Disease Burden

Due to its fast rising incidence, diabetes has been labeled an epidemic in the United States. According to the 2011 statistics out of the Center for Disease and Control (CDC) and the American Diabetes Association (ADA) there are 25.8 million Americans with diabetes and 7 million of those are undiagnosed. In addition, 79 million Americans have pre-diabetes defined as having an impaired fasting blood glucose of 100-124mg/dl or impaired glucose tolerance with 2 hour post prandial blood glucose 140-199mg/dl.(1) It is now estimated that by the year 2050 one in three Americans will have diabetes. (1)

As expected the cost burden of diabetes is also rising, having increased from $147 billion/year in 2007 to $245 billion/year in 2011.This includes direct medical costs of $175 billion and indirect costs of $69 billion. California leads the nation with the largest population of diabetics with the associated costs of $27.6 billion/year. The ADA reports that 43% of the national medical costs of diabetes are attributed to inpatient hospital costs; Medicare, Medicaid and the military pay for 62.4% of these costs.(1)

Inpatient glycemic management has captured the attention of the healthcare industry since the publication of several landmark studies that demonstrated multiple benefits of tighter glycemic control in hospitalized patients. (2-3) Uncontrolled diabetes or hyperglycemia in the hospitalized patient is associated with lengths of stay that are 20-40% longer than hospitalized patients maintained in euglycemia, as well as 14-20% higher readmission rates.(1)

There is growing evidence that our healthcare system will be inundated by the sheer volume of individuals with diabetes and the economic impact of their care. Currently, it is estimated that one in every four patients admitted to a hospital has diabetes.

Background: Is Glycemic Management Important for Hospitalized Patients and the Hospital?

Research suggesting there is benefit of tight glucose control in hospitalized patients emerged in 1998 with studies published by Furnary, et al (2) and studies published by Van den Berghe, et al in 2001.(3) Since these publications there have been multiple studies published also demonstrating the benefits of glucose management in the hospitalized patient.The benefits described in these studies include reduction in sepsis, improved wound healing, reductions in mortality and improvements in length of stay. (2-7) What differs in these studies is the glycemic target recommendations. The treatment targets vary from ranges of 70-110mg/dl to higher targets of 140-180mg/dl.The common thread in the studies published to date is the understanding that tighter glycemic control needs to be accomplished in the safest possible manner to prevent and minimize the risk for hypoglycemia.

Hyperglycemia in the hospitalized patient is most common in those patients with diabetes. Many times

these patients arrive with poor glycemic control, or become hyperglycemic due to the stress of the admitting illness. Many patients without diabetes experience hyperglycemia episodes during their hospitalization. This is primarily related to the stress of the admitting illness. Medications (especially glucocorticoids), over or under nutrition, surgery, dialysis solutions, hypothermia and anesthesia can also contribute to hyperglycemia in patients with or without diabetes. The metabolic changes triggered by the stress of illness increase insulin resistance due to an increased production of the counter-regulatory hormones, glucagon, epinephrine, cortisol and growth hormone. Add to this a reduction of insulin secretion that cascades into higher plasma glucose, free fatty acids, ketones, lactate and inflammatory cytokines. These changes in metabolism can lead to neutrophil dysfunction, catabolism, cardiac perfusion injury, inflammatory pathway activation, endothelial dysfunction, thrombotic tendency and tissue injury.

While these alterations in glucose metabolism result in poorer outcomes and higher costs of care, there is strong evidence that the appropriate treatment approach to in hospital hyperglycemia can improve outcomes and reduce health care costs. Levetan, et al reported significant cost savings of $2353 per patient and a 56% reduction in length of stay when an endocrine consult and diabetes team were utilized to assist in the glycemic management of hospitalized patients with diabetes. (5) In the DIGAMI Study, Malmberg et al reported a mean increase of $2824 in hospital charges for every 50mg/dl increase in blood glucose in patients hospitalized for coronary artery bypass graft (CABG) surgery. (7) When we understand the risk of poorer clinical outcomes and the cost of hyperglycemia can we afford to ignore glucose management in the hospital setting?

Inpatient Glycemic Management Guidelines

Recommendations for safe, practical and achievable glycemic targets have been published by a variety of professional organizations including the American Diabetes Association (ADA), American Association of Clinical Endocrinology (AACE), the American College of Physicians (ACP) and the Society of Hospital Medicine (SHM). A summary of guidelines from these resources are described in Table 1. All the guidelines discourage the use of sliding scale insulin as the sole means to manage blood glucoses in the hospitalized patient. Instead, a regimen of basal-bolus insulin therapy should be instituted and adjusted daily to achieve glycemic targets. While early studies suggested very strict glucose targets in the intensive care unit, current consensus is that blood glucose between 140 and 180 mg/dL is an appropriate target in the critically ill patient. The consensus on glycemic targets at this time in the non-critical hospitalized adult is <140 mg/dL fasting or pre-meal, and <180 mg/dL on any random glucose measurement. Hypoglycemia (defined as glucose <70 mg/dL) prevention and treatment should be standardized across the institution and all staff should be trained on insulin therapies and hypoglycemia prevention and management.

Some general rules in the practical approach to inpatient hyperglycemia

In most patients oral anti-diabetic drugs should be stopped on admission due to the possibility of side effects and drug-drug interactions. In contrast to oral drugs, insulin treatment offers much greater flexibility in dosing, can be given in both kidney and liver failure,

Table 1 Glycemic Management Recommendations

Recommendation	ADA	AACE	ACP	SMH
Use of sliding scale insulin	Strongly discouraged	Strongly discouraged	Relatively ineffective	Strongly discouraged
Basal insulin +bolus (nutrition+correction)	Strongly encouraged	Strongly encouraged	No recommendations	Strongly encouraged
Glycemic Targets	Premeal<140mg/dl Random<180mg/dl	Premeal<140mg/dl Random<180mg/dl	140-200mg/dl in MICU/SICU and Avoid targets <140mg/dl for IV insulin therapy	No glycemic targets recommended
Hypoglycemia	BG<70mg/dl Hypoglycemia Protocol for standardized treatment & prevention	BG<70mg/dl Hypoglycemia Protocol for standardized treatment & prevention	No recommendations	BG<70mg/dl Hypoglycemia Protocol for standardized treatment & prevention

has no drug-drug interactions, and results in few side effects except for hypoglycemia. In the intensive care unit, hyperglycemic patients should be placed on a continuous insulin infusion targeting a glucose level between 140 and 180 mg/dL. Several protocols for this type of treatment are available and treatment in the intensive care unit will not be discussed further in this review. On the general ward, sliding scale insulin should be avoided as this type of approach is based on chasing the glucose abnormality and will never result in optimal control. In patients with type 1 diabetes, sliding scale insulin is considered dangerous, having resulted in the development of diabetes ketoacidosis in several instances. Patients with hyperglycemia who are not known to be diabetic should have hemoglobin A1C measured on admission to determine if they have undiagnosed diabetes; this will help determine who will need diabetes teaching as part of the hospitalization and a long-term diabetes follow-up.

Blood glucose value higher than 180 mg/dL should be the trigger for instituting insulin treatment on the general ward. In estimating the insulin requirements of diabetic patients on the general ward, there is strong empirical evidence that most diabetic patients will require between 0.3-0.5u/kg/24h. Some non-diabetic patients with stress hyperglycemia might have lower insulin requirements while some type 2 diabetics with insulin resistance may have higher insulin requirements. Approximately half of the insulin dose should be administered as basal (long acting insulin) insulin and half should be administered with meals (as short acting insulin). Glucose levels should be measured by finger stick before the first meal (fasting), before all other meals, and before sleep; more frequently if needed. The fasting blood glucose value is the best reflection of the adequacy of the long acting insulin dose; its dose should be adjusted primarily according to the fasting blood glucose value. The pre-meal blood glucose should be used to determine the supplemental insulin (on top of the meal insulin) to be given for each meal as fast acting insulin. In addition, it can be useful to assess 1-2 h postprandial glucose values to evaluate the fast acting meal insulin doses. Using this approach, a patient eating three meals a day will be receiving long-acting insulin once a day (for example 15u) and fast-acting insulin before each of his three meals (for example 5u three times a day with a pre-determined supplement that takes into account pre-meal hyperglycemia). The goal of treatment is to keep most pre-meal glucose values less than 140 mg/dL and all other glucose values less than 180 mg/dL; if most glucose values exceed these targets insulin doses need to be increased. At the same time, it is important to avoid hypoglycemia and blood glucose values less than 70 mg/dL call for a decrease in insulin dosing.

The approach described above assumes that the patient is eating meals. Many patients in the hospital, however, are receiving parenteral or enteral nutrition and in these cases the approach needs to be modified. The best treatment in patients receiving parenteral nutrition is to include insulin in the infusion. For continuous enteral nutrition the approach is usually based on long acting insulin (for example NPH insulin given every eight hours) with supplemental fast acting insulin given every four to six hours as needed according to blood glucose.

Discussion: Developing Inpatient Glycemic Management Strategies

Establishing a systems approach to managing hyperglycemia and preventing hypoglycemia in the hospital requires the support of hospital administration and a multidisciplinary team dedicated to improving the care of patients with hyperglycemia and/or diabetes.

The interdisciplinary team should include representatives from physician groups, nursing, pharmacy, nutrition, case management, information services and quality improvement that are authorized to:

- Assess the institution's current practices, protocols and procedures around glycemic management and formulate a gap analysis.
- Establish glycemic targets for all inpatient populations, i.e. noncritical adults, critical care, obstetrics, pediatric.
- Develop policies, procedures, guidelines, algorithms, clinical pathways and order sets that guide the clinical staff towards process improvements in the glycemic management of the hospitalized patient.
- Provide ongoing education for medical and clinical staff on diabetes and glycemic management.
- Identify deficiencies and areas for improvement as part of the institution's performance improvement processes.
- Report outcomes to hospital administration on a regular basis.

Managing hyperglycemia and diabetes in the hospital requires a broad approach that includes a variety of

"stakeholders" and provides for patient safety and efficacy of treatment.

Conclusion :Resources for Inpatient Glycemic Management/Standards

Hyperglycemia in the hospitalized patient is associated with poorer outcomes and can be a costly burden to the health care system. Developing and implementing a robust system for glycemic management in the hospital setting can improve patient outcomes and reduce costs. Guidelines and tools are available that can assist multidisciplinary teams to address glycemic management and implement policies, protocols, algorithms, standardized order sets and staff education and achieve safe glycemic targets for the hospitalized patient with hyperglycemia.(4, 8-9) Such algorithms can be built into the hospital's electronic medical record and order system to enhance compliance with the best possible practices in treating inpatient hyperglycemia.

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ON MODERN DIAGNOSIS OF HYPERPARATHYROIDISM

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Definition of Hyperparathyroidism

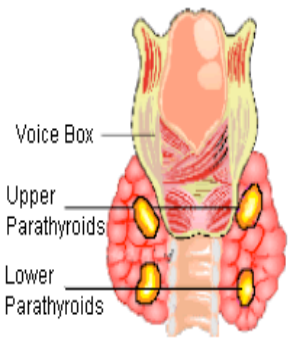
Hyperparathyroidism means excessive secretion of Parathyroid hormone. This can be classified as following:

1. Primary Hyperparathyroidism
2. Secondary Hyperparathyroidism
3. Tertiary Hyperparathyroidism

In this article, my review will concentrate on the most common type -- primary hyperparathyroidism.

Symptoms and Diagnosis of Hyperparathyroidism

Starting early in 1970, when we are ordering a routine automated chemical panel, more hypercalcaemia have been detected. At the same time, we have found more and more hyperparathyroidism. It is not clear whether the incidence is really rising. Parathyroid hormone (PTH) is needed in regulation of calcium in bones. It also maintains proper absorption of calcium and phosphate from the gut. Excessive PTH can affect functions of the target organs.



The Rear View of Parathyroids

When Albright(1) and Martin(2) first described it in 1940 and 1942, the disease presented very late with the effects being on the bones .The patients had severe bone pain, kidney stones and also brown tumors. Some patients can be asymptomatic. Other patients may complain of body aches. Patients may have osteoporosis, kidney stones and hypertension. Family history and nutritional history need to be taken. Hyperparathyroidism runs in families. Symptoms of hypercalcemia may depend on the level of calcium. Patients with hypercalcemia usually experience bone pain, fatigue and loss of height. Occasionally, patients with abnormally high calcium can be asymptomatic. Higher calcium levels can also cause polyuria, nocturia and obtundation.

Physical examination of the neck rarely will demonstrate a nodule. If a patient's thyroid is enlarged and nodular, differentiation between the thyroid and parathyroid on physical exam may be difficult. There may be hypertension. Careful height measurement will help in diagnosis of osteoporosis.

Laboratory tests should include a comprehensive metabolic panel, the ratio of calcium and PTH, a 24-hour urine calcium, a level of Vitamin D and a bone density evaluation.

Management of Hyperparathyroidism

The treatment of PHTH is surgery. Of course severe hypercalcaemia will need to be addressed initially. Symptomatic patients with severe hypercalcaemia should have surgery done as soon as possible to avoid the deleterious effects on the target organs.

Recent studies have demonstrated that even the patients with asymptomatic

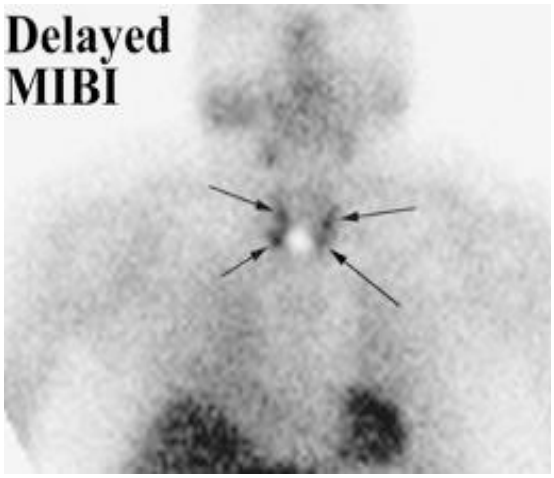
hyperparathyroidism can benefit from surgery(3). Certain factors have been considered as the indications for surgery. These are:

1. Patients' age younger than 50
2. Patients' Creatinine clearance reduced by 30 % corrected for age
3. Patients with Kidney stones
4. Patients with persistently high serum calcium or
5. Patients' calcium > 400mg on 24-hour urine collection
6. Patients' bone density reduced by more than 2 standard deviation for age-matched controls

Nowadays, it is still a frequent problem in identifying the location of the parathyroid glands. It is difficult to localize even with the best of imaging. The number of parathyroid glands in a normal person may be from 4 to 6 in total. The location of our parathyroid glands may be anywhere from the neck (mostly behind the thyroid) to the mediastinum. Over the years parathyroid surgery has been deemed exploratory because of the difficulty in localizing the gland before surgery. Successful parathyroid surgery depends on the experience of the parathyroid surgeon as well as localizing methods. To avoid bilateral exploratory surgery, the surgeon may need to look for more carefully. Patients having a nodular thyroid will need more imaging to identify the parathyroids and to separate them from the thyroid. Traditionally, ultrasound alone is not enough in diagnosis of parathyroid adenoma. Recently, many centers are using a combination of ultrasound and nuclear scanning with either technicium or sestemibi.

Ultrasound of the neck may identify a mass or nodule but it may be difficult to separate it from the thyroid unless the user is experienced.

Combination of ultrasound and MIBG (Meta iodo benzo guanidine) nuclear scan has helped. Using Tc-MIBI (Methoxyisobutylisonitrile) plus oral potassium perchlorate (KCLO4)subtraction scintigraphy to separate thyroid nodules from parathyroid glands is now a new trend since the oral KCLO4 makes rapid washout of Tc-MIBI. Minimally invasive surgery will be successful if the preop imaging is accurate and predictive. From a study of 143 patients in Italy published in 2001(1), the accuracy was above 90 % and also can predict whether it's a multiglandular disease or a single parathyroid adenoma.



Unfortunately sestemibi scan by itself may be unable to find the parathyroid glands. This may mislead some patients to miss surgical treatment. With a thorough pre-operative localization of parathyroid glands, surgical treatment is usually successful in most of cases if surgery is performed by an experienced parathyroid surgeon. Intraoperative PTH levels are also very helpful guidepost for proceeding of operation.

Postoperatively patients should do well with calcium levels dropping to the normal range. In some cases there may be hypocalcaemia which can be easily discovered and corrected to satisfactory range.

Postoperatively, if the patient's calcium and PTH levels are persistently high, then it will be due to misdiagnosis or poor localization of parathyroid glands before surgery.

Medical treatment is indicated only in the very elderly or when the patients are poor candidates for surgical intervention.

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CURRENT MANAGEMENT OF PITUITARY ADENOMAS

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Introduction

Benign tumors of the pituitary gland, known as pituitary adenomas, are being diagnosed with greater regularity within our general patient population. While small, clinically insignificant pituitary adenomas may be present in as many as one in six people, the rate of clinically relevant tumors based on either size or symptomatology is approximately 1 out of every 1064 individuals 1,2. They currently represent the third most commonly diagnosed brain tumor amongst all people and the most common in ages 15-34.3 Tumors of the pituitary may either over-secrete a normal hormone of the anterior gland (functional adenomas) or be non-secreting null-cell tumors (non-functional adenomas). Both types may present with varying degrees of pituitary dysfunction (hypopituitarism) or compromise of the adjacent optic nerves/chiasm as a result of direct tumor compression. Overall, the optimal diagnosis and management of patients with pituitary adenomas requires a multidisciplinary approach with contributions from endocrinologists, radiologists, ophthalmologists, otolaryngologists, neurosurgeons, and radiation oncologists.

Transsphenoidal Surgery for Pituitary Adenomas

During the past 100 years, the surgical approach to pituitary adenomas through the sphenoid sinus (transsphenoidal approach) has experienced significant advancement as a result of technological innovations and modernization of surgical technique within the field of neurosurgery. The Austrian neurosurgeon Dr. Hermann Schloffer is believed to be the first to have removed a tumor of the pituitary gland via a transnasal route in 1907.4 Further progress was made by Dr. Harvery Cushing, often called the "Father of Neurosurgery," who performed the operation on over 200 patients with pituitary tumors between 1910 and 1925.5 The technological limitations of the time, however, combined with a growing preference for transcranial approaches to the sellar region led to underutilization of the transsphenoidal approach by the neurosurgery community for the next 30-40 years 4-6.

A renewed interest in the transnasal route to pituitary adenomas developed during the 1950s and 1960s, coinciding with two important innovations in neurosurgical operative technique. Jules Hardy, a Canadian neurosurgeon, sought to improve on the lack of adequate illumination and magnification available for all neurosurgical procedures with the introduction of the operating microscope 6. This was especially beneficial in transnasal surgery because of the long reach and narrow corridor associated with the approach. Among other things, this allowed for significant improvements in the overall success of the procedure. Surgeons were now able to perform selective adenomectomies of all pituitary tumors, including functional microadenomas (tumors < 1 cm), with the goal of removing the entire tumor while preserving the normal gland 4. The second innovation, by Gerard Guiot, involved the use of intraoperative fluoroscopy, which provided real-time image guidance of the location and position of instruments during the transsphenoidal procedure 7. Both of these advancement contributed to reducing the overall morbidity and mortality of the transsphenoidal

approach to the sella. In combination with improvements in microsurgical instrumentation, the subsequent years also saw an expansion in the breadth of the procedure with neurosurgeons also utilizing the approach to access other tumor types, such as meningiomas, schwannomas, and craniopharyngiomas located within the anterior skull base, suprasellar, and cavernous sinus regions 4,8.

Further progress using the transsphenoidal approach to pituitary adenomas has occurred over the past 25 years with the increased utilization of the endoscope in neurosurgical procedures. As compared with the operating microscope, the endoscope obviates the need for the nasal speculum during transsphenoidal approaches to the sellar region, thus expanding the overall surgical corridor and allowing for greater instrument maneuverability. In addition, endoscopy, especially with the use of an angled lens', provides superior illumination of the operative field, a wider panoramic view, and improved visualization of the more lateral, superior, and inferior areas which are not in a direct line-of-sight 9. While some neurosurgeons had previously experimented using the endoscope in a variety of procedures throughout the first half of the 20th century 10-12, it was the introduction of the modern design with a rigid rod–lens system, along with advances in image quality and illumination, that led to more widespread acceptance and improved overall outcomes when utilized either as an adjunct to the operating microscope or as the primary visualization source 13-16.

With regards to pituitary adenoma surgery, the use of the endoscope has gained widespread acceptance and has led to increased collaboration with otolaryngologists for assistance both with the initial approach through the nose as well as in skull-base repair for intraoperative cerebrospinal fluid (CSF) leaks after tumor removal. The first series describing successful removal of pituitary adenomas using a purely endoscopic approach were published in the 1990s 17,18. Subsequently, as neurosurgeons have become more comfortable with endoscopic visualization, many have transitioned first to an endoscopic-assisted (combination of endoscope and microscope) and eventually to a fully endoscopic approach to pituitary adenomas with overall favorable results 19-22. Enhanced visualization with high-definition (HD) cameras, intraoperative stereotactic navigation, new endoscopic-specific instrumentation, and more reliable skull-base closure techniques that reduce postoperative CSF leak rates have further improved the effectiveness of the approach, while establishing endoscopy as one of the more rapidly advancing specialties in neurosurgery 15.

Prolactinomas

Prolactin-secreting pituitary adenomas comprise over 60% of clinically significant tumors of the pituitary gland 1. Symptoms in women of childbearing age related to elevated serum prolactin include amenorrhea, galactorrhea, weight gain, and infertility. In men, symptoms are often much more subtle and may include varying degrees of impotence, reduced libido, infertility, and low testosterone 23. As a result, prolactinomas are often diagnosed at a much later stage in men, and there is some evidence to suggest that the overall characteristics of these tumors make them somewhat more aggressive and more resistant to medical therapy as compared to those in women.24

Once diagnosed, first-line treatment for symptomatic prolactinomas continues to be with dopamine agonist medication, primarily cabergoline or bromocriptine. Biochemical remission rates with normalization of serum prolactin have been reported to be as high as 76% in patients treated with bromocriptine and 89% in patients treated with cabergoline, with tumor reduction rates of >50% in 64% and 96% of treated patients, respectively 25-27. Overall, both medications are generally well-tolerated in patients undergoing treatment; the most common complaints are headache, dizziness, nausea, and vomiting, especially after initially starting the medication 28. Side effects related to prolonged treatment with dopamine agonists are minimal, although there may be some increased risk of developing new cardiac valve regurgitation in patients who receive long-term cabergoline 29. Monitoring with serial echocardiograms is often recommended. Discontinuation of treatment may be indicated in patients who have had complete resolution of their tumors on imaging, but close monitoring is necessary as recurrence rates have been reported to be as high as 63% 30.

Surgical resection of prolactinomas via a transsphenoidal approach is indicated in patients who are intolerant of dopamine agonist therapy as a result of severe side effects as well as in those who demonstrate tumor resistance to treatment. There is some debate as to whether or not patients who have had rapid visual loss from tumor growth or an episode of tumor apoplexy (tumor hemorrhage or infarction) should also proceed straight to surgical resection, although it is even reasonable to try these patients on a course of medical therapy first. Patients can be considered medication-resistant if the prolactin level fails to normalize or if the tumor does not demonstrate a reasonable decrease in size after at least

12 months of treatment 26,31. Rates of resistance may be as high as 24% with bromocriptine and 11% with cabergoline treatment 32.

Surgical resection of prolactinomas is most effective, with remission rates up to 90%, for tumors located either completely within the confines of the sella or with only moderate suprasellar extension. In tumors with extensive invasion of the suprasellar or cavernous sinus regions at the time of diagnosis, complete tumor resection is much more challenging and is associated with remission rates of <50% following surgery 33. Multimodality therapy after cytoreductive surgery, either with dopamine-agonist medication or with stereotactic radiosurgery (SRS)/ stereotactic radiotherapy (SRT) to the residual tumor, is typically indicated in these patients. Preoperative and immediate postoperative prolactin levels can be predictive of overall remission rates following surgery and should be monitored carefully. Preoperative levels of >601 ng/ml are associated with surgical remission rates of only 12.5% while levels <200 ng/ml, as seen with less invasive smaller tumors, have remission rates over 85%. In addition, favorable 5-year remission rates of 98% are seen in patients with postoperative day 1 prolactin levels <10 ng/ml as compared to only 12% with postoperative day 1 levels >10 ng/ml, indicating the likely presence of residual tumor.34

Cushing's Disease

Cushing's disease is characterized by abnormally high levels of serum cortisol as a result of excessive production of adrenocorticotrophic hormone (ACTH) from a functional pituitary adenoma. The detrimental effects of chronic hypercortisolism include weight gain, central obesity, hypertension, diabetes mellitus, and hyperlipidemia, all of which contribute to a fourfold greater risk of mortality from cardiovascular complications in these patients 35-37. Other features of Cushing's disease include muscle weakness, round face or "moon facies," acne, hirsutism, fat deposition on the back of the neck or a " buffalo hump", abdominal striae, easy bruising, depression, and cognitive impairment 38,39. As a result of the high morbidity and mortality associated with uncontrolled Cushing's disease, treatments are focused on normalizing the serum cortisol level while minimizing the risk of recurrence, reducing any associated tumor mass-effect symptoms, and preserving normal pituitary function.

The symptoms typical of Cushing's disease, while characteristic in most patients, are nonspecific for the disease. In addition, ACTH-secreting pituitary microadenomas may often present on magnetic resonance imaging (MRI) as only small hypoenhancing regions within the pituitary gland or may be microscopic and completely undetectable by imaging 40. Diagnosing Cushing's disease and differentiating it from Cushing's syndrome as a result of ectopic ACTH secretion can present a significant challenge to the clinician, thus requiring a thorough diagnostic work-up for each patient. Initial evaluation in patients with suspected Cushing's should be with an 11 p.m. salivary cortisol check, as this is considered to be the most sensitive marker for abnormal serum cortisol levels 41. If the levels are elevated, confirmation is made with a 24-hour urinary free cortisol (UFC) test, which has shown a sensitivity of up to 100% and specificity ranging from 94% to 98% in accurately diagnosing Cushing's disease 42,43. Further confirmation can be made with a repeat 24-hour UFC or with a low-dose (1 mg) dexamethasone suppression test.

Once it has been established that the patient has persistent elevated serum cortisol that is not from exogenous steroid use, the cause of the elevation must be determined. Low serum ACTH levels indicate a primary adrenal source for the hypercortisolism, and abdominal imaging is indicated. High ACTH levels indicate either an ACTH-secreting pituitary adenoma (Cushing's disease) or ectopic ACTH secretion 40. These can sometimes be differentiated with a high-dose dexamethasone suppression test, although the accuracy of the test in suppressing pituitary ACTH secretion only is variable 44-46. If Cushing's disease is suspected, patients should undergo an MRI of the pituitary region. In cases where no definitive tumor is detected on MRI, inferior petrosal sinus sampling (IPSS) is indicated. IPSS involves angiographic sampling of the immediate venous drainage from the pituitary gland. A central-to-peripheral ratio of ACTH >2 prior to stimulation with corticotrophin-releasing hormone (CRH) and >3 afterwards is highly correlated with a pituitary source for the patients Cushing's.47

Transsphenoidal surgery for tumor resection remains the primary therapeutic option in patients with newly diagnosed Cushing's disease. Long-term remission rates range between 59% and 98%, with higher rates found in patients with microadenomas and lower rates associated with larger and more invasive macroadenomas 48-54. Recurrence despite initial evidence of remission is also seen following surgery and may be as high as 27% with longer follow-up times 55. Overall, achieving postoperative serum cortisol levels ≤3 μg/dl by 72 hours is highly predictive of long-term remission 55,56. In those

patients who do not show immediate signs of remission, early reoperation within 60 days may achieve long-term remission at a rate of up to 68% as long as residual tumor is not present within the cavernous sinus 57,58.

In patients with recurrent or refractory Cushing's disease despite attempted tumor resection, medical therapy or bilateral adrenalectomy represent secondary options for treatment. Surgical adrenalectomy, while effective at definitively eliminating serum hypercortisolism, relegates the patient to permanent glucocorticoid and mineralocorticoid replacement therapy and carries a 30% risk of Nelson's syndrome, or aggressive unregulated growth of a pituitary corticotroph adenoma 59. Recent focus therefore has been directed primarily towards the development of effective medical treatments for Cushing's.

Pasireotide is a somatostatin analog with an affinity for receptors expressed by ACTH-secreting cells of the pituitary 60. In a phase III multicenter trial,61 patients with Cushing's disease refractory to treatment, recurrent tumors, or de novo tumors in patient's ineligible for surgery were all treated with 12 months of pasireotide. Normalization of UFC was seen in up to 26% of patients. Associated improvements in blood pressure, body weight, and quality of life were also observed. Hyperglycemia and elevated hemoglobin A1C levels have been observed in patients taking pasireotide, so careful monitoring of blood glucose is necessary during treatment. Other pituitary gland–directed therapies such as the dopamine receptor agonists, peroxisome proliferator-activated receptor-gamma (PPAR) ligands have also shown some effectiveness in treating refractory Cushing's disease but thus far are used only infrequently and require further confirmatory investigations 60.

The glucocorticoid receptor antagonist mifepristone is another medical treatment for Cushing's disease used specifically to manage the clinical effects associated with long-term hypercortisolism. Improvement in glucose tolerance, diabetes, high blood pressure, and body weight have all been found with mifepristone treatment 62. Because serum cortisol levels do not change with receptor antagonist therapy, treatment response assessment must be based on improvements in clinical features. In addition, there is no effect on existing tumor size or in preventing new tumor growth.The final group of medications used in the treatment of Cushing's disease are those that inhibit cortisol synthesis from the adrenal gland. Ketoconazole and metyrapone are both steroidogenesis inhibitors that have demonstrated effectiveness in normalizing serum and UFC levels in patients with Cushing disease 63,64, although long-term treatment may have some liver toxicity, and, as with bilateral adrenalectomy, there is no effect on the pituitary tumor itself.These medications should be reserved for symptomatic treatment after non-curative surgery60.

In addition to medical therapy, radiation treatment with single (SRS) or fractionated (SRT) dosing can be effective for invasive or recurrent ACTH-secreting pituitary adenomas not cured with initial surgical resection. Remission rates for SRS typically range between 50% and 70%, with good tumor control rates and varying rates of recurrence after initial cure 65-68. New hypopituitarism is an accepted risk of radiation, occurring up to 36% of the time, most commonly in patients without obvious tumor on MRI who require treatment directed towards the entire sella 69. Cranial nerve deficits including optic neuropathy are minimized with stereotactic radiation. While the risk of a new deficit is typically <5%, it is highly dependent on the degree of tumor invasion and the overall proximity to the nerves during treatment, and is typically higher in patients who have undergone previous radiation therapy to the region 70.Although SRT is associated with longer time periods to remission, it is often preferred in patients with invasive tumors to minimize the radiation dose to the surrounding structures 71,72. Overall, radiation therapy is highly effective as an adjunctive treatment and should be considered when necessary in all patients with refractory Cushing's disease.

Acromegaly

Acromegaly is a systemic disorder, typically occurring from overproduction of serum growth hormone (GH) from a functional pituitary adenoma.They account for approximately 13% of all clinically significant pituitary tumors 1. GH mediates its effects on the body through the stimulation of insulin-like growth factor-I (IGF-1) secretion from the liver. Soft tissue and bony overgrowth from prolonged serum IGF-1 elevation in adults produces characteristic external features of acromegaly including coarse facial features, prominence of the jaw (prognathism), macroglossia, wide nasal bridge, widening of the spaces between the teeth, frontal bossing, and enlarging hands and feet 73. In children, before closure of the long bone epiphyseal growth plates it presents as gigantism.Along with symptoms related to local tumor mass effect from a GH-secreting pituitary adenoma, patients with uncontrolled acromegaly are also at risk for hypertension, diabetes, hypertrophic cardiomyopathy, hypertrophic arthropathy, obstructive sleep apnea, and

carpal tunnel syndrome 73. Because these patients have a mortality rate 2–4 times higher than the general population, the goal of treatment is to reduce the serum GH level (fasting level <2.5 μg/L) in order to eliminate the detrimental effects of IGF-I overproduction.74

The diagnosis of acromegaly is made through the detection of elevated serum IGF-I levels along with a GH level that fails to decrease below 1 ng/ml after a 75-g oral glucose tolerance test (OGTT) 75. Criteria for remission following treatment includes normal serum IGF-I level, random GH level <1 ng/ml, and GH level <0.4 ng/ml following OGTT 76. Surgical resection of the pituitary adenoma via a transsphenoidal route remains the primary treatment in all patients with acromegaly who have no significant contraindications to surgery. Remission rates following surgery are highly dependent on tumor size and degree of cavernous sinus invasion at the time of initial diagnosis. Overall remission rates range between 40% and 80%, with rates >70% for most tumors <2 cm and <50% for tumors >2 cm. With regards to the invasiveness of the tumor, those with minimal to no cavernous sinus invasion can have remission rates over 80%. This decreases to <35% with high degrees of cavernous sinus invasion even with the use of the endoscope during surgery 77. Immediate postoperative (day 1 or 2) serum GH levels <2.5 ng/ml are highly predictive of future remission 77.

For acromegalic patients who do not achieve full remission after surgery as well for those who are not surgical candidates or who exhibit recurrence following a period of remission, adjuvant treatment options include medical therapy or SRS/SRT. Medical treatment involves the use of somatostatin analogs (SSAs), peripheral GH receptor antagonists (GHRAs), and dopamine D2 receptor agonists. Somatostatin is a native hormone that, among other functions, inhibits the secretion of GH from somatotrophic cells in the anterior pituitary gland. SSAs act at somatostatin receptors, with the goal of decreasing serum GH levels and associated IGF-1 synthesis from the liver. Long-acting SSA formulations are currently available including octreotide LAR and lanreotide Autogel, both of which require injections every 28 days 78. Overall, the medications are well tolerated, with abdominal discomfort and hyperglycemia being the most commonly reported side effects 79. Control of GH and IGF-1 levels occurs in 48–75% of patients treated with SSAs after initial failed surgery or radiation80-83. In addition, primary treatment with SSAs on initial diagnosis has demonstrated similar GH and IGF-1 control rates, with >25% tumor size reduction in over 80% of patients 84,85. Further investigation into pretreatment with SSAs prior to surgery is ongoing, with studies so far showing some reduction in surgical risk but with questionable improvements in overall outcomes 86,87.

In patients who do not respond to or are intolerant of SSA therapy including those who develop worsening glucose intolerance, the peripheral GHRA pegvisomant is also effective for the treatment of acromegaly. Administration is via daily subcutaneous injections; the main side effects are related to injection site irritation and impaired liver function tests, but glycemic control is improved as compared with SSAs 88,89. IGF-1 normalization has been seen in over 90% of patients treated with pegvisomant only, and it may also increase the response to SSA treatment if added as a secondary therapy 90,91. As a result of its mechanism of action, however, pegvisomant does not inhibit GH secretion and thus does not stimulate tumor shrinkage. Regular monitoring with serial MRI scans is therefore important in patients being treated with pegvisomant, although it has not been previously associated with high degrees of tumor growth 92. Dopamine agonists such as bromocriptine and cabergoline were previously used as the primary medical treatment to suppress GH secretion in patients with acromegaly, but they have since been replaced by SSA therapy, which has shown to be a more effective option. Dopamine agonists are currently utilized only as an adjunct to existing SSA treatment to improve responsiveness in patients with inadequately controlled disease or for patients with combined prolactin- and GH-secreting pituitary adenomas 93. Finally, initial surgical debulking has an important role in invasive tumors, and evidence suggests that these tumors show an improved response rate to SSA therapy after partial surgical resection 94,95. Therefore, unless contraindicated, surgery should be considered for all patients with diagnosed acromegaly prior to beginning medical treatment.

SRS or SRT following surgical resection is indicated for residual tumor that is resistant to medical therapy as well as for invasive recurrent tumors. One study, which evaluated treatment with gamma knife radiosurgery (GKRS) after failed transsphenoidal tumor removal, demonstrated an IGF-1 normalization rate of 53% with a tumor volume control rate of 92% after a mean 57-month follow-up 96. Using various criteria, others have reported hormonal remission rates in up to 82% of acromegalic patients treated with either GKRS or linear accelerator (LINAC)–based radiosurgery 97. The main side effect associated with radiation treatment to this region is the development of new hypopituitarism, which occurs in up to 47% of patients. Damage to the optic apparatus,

new cranial neuropathies, or radiation necrosis of the surrounding brain are also reported but may be minimized with dose fractionation (SRT) 97. SRS and SRT therefore represent valuable treatment options for refractory GH-secreting tumors and may be safely utilized with minimal radiation directed towards the surrounding cranial nerves and normal brain.

Pituitary Incidentalomas

Incidentally discovered pituitary adenomas are previously unsuspected pituitary lesions found on brain imaging performed for another unrelated reason. All patients with pituitary incidentalomas should initially undergo a full pituitary hormonal evaluation to rule out the presence of a functional tumor as well as to determine if there is evidence of pituitary dysfunction from the lesion. As a result of the subtle systemic effects associated with partial hypopituitarism especially in men, hormonal deficiencies may go unrecognized for long periods of time. Previous studies have shown partial anterior pituitary gland failure secondary to tumor compression in 41% of patients with incidentally discovered lesions. In addition, 15% of patients were found to be men with prolactinomas 98. Visual field deficits and other mild visual abnormalities may also go unnoticed by patients or be attributed to other causes. In the same study, varying degrees of visual field alterations were discovered in 22% of patients with incidentally discovered lesions 98. Therefore, all patients who demonstrate evidence of tumor compression of the optic nerves/chiasm should be sent for detailed ophthalmologic evaluation.

Once a full endocrinologic and ophthalmologic work-up has been completed, the patient and physician must decide whether to monitor the incidentally discovered lesion conservatively with serial imaging or to treat immediately. Multiple retrospective studies of patients with incidentalomas have demonstrated average growth rates of approximately 10% in microadenomas (<1 cm) and 24% in macroadenomas (≥1 cm), with some reporting rates as high as 50% 99,100. Tumor enlargement along with new symptom onset may occur in up to 20% of patients, especially in those with tumors >1.5 cm. Furthermore, pituitary apoplexy (tumor hemorrhage or infarction), which may result in acute visual loss, ophthalmoplegia, or hypopituitarism, has been reported in up to 10% of incidentalomas with average 5-year follow-up 99.

The Endocrine Society Clinical Guidelines101 for patients with pituitary incidentalomas recommend surgery or medical treatment for any patients with evidence of visual field deficits or other visual abnormalities from tumor compression or with a history of apoplexy. Surgery should be considered if there is documented growth of the lesion on serial imaging, new loss of pituitary function, or tumor adjacent to the optic nerves/chiasm and there is a plan for pregnancy. If the criteria for surgery are not met, it is recommended that tumors be monitored with serial MRIs every 6 months to 2 years. Pituitary function testing should be obtained every 6 months initially and yearly after that as well as at any time where there is evidence of new tumor growth. Enlarging tumor with new compression of the optic nerves/chiasm should prompt an immediate ophthalmologic evaluation. New imaging should always be obtained with the development of any new signs or symptoms. Finally, because of the high tumor growth rates and chance of new symptom development, surgery should be considered initially in all younger patients with incidentally discovered tumors >1.5 cm in largest tumor diameter.

Future Considerations

Significant progress continues to be made in the treatment of pituitary adenomas. New advances in imaging techniques have allowed for better preoperative tumor localization while the use of intraoperative MRI technology has shown some benefit in improving overall tumor resection rates 102,103. As previously discussed, tumor visualization especially at the extreme borders of the sellar region, has been enhanced with the introduction and widespread acceptance of the endoscope in pituitary adenoma surgery. One of the main limitations of endoscopy until now, however, has been that visualization was only in two dimensions. Without stereoscopic vision, the surgeon must depend on monocular clues such as motion parallax, size, and perspective to understand object depth. Theoretically, this lack of depth perception may reduce the speed and accuracy of an endoscopic procedure. The use of three-dimensional (3-D) endoscopes remains in the early stages of development, but preliminary studies have shown comparable surgical results to those achieved with 2-D endoscopy but with a subjective improvement in overall depth perception 104. Additional modifications in 3-D visualization along with increased miniaturization and improvements in the structure and design of the current endoscope models will no doubt continue to impact and further advance pituitary adenoma surgery in the coming years.

In considering the future of medical and radiation therapy for pituitary adenomas, as progress continues to be made in improving their overall effectiveness and safety profile, these are likely to become more commonly used components of the treatment regimen. In fact, it may only be a matter of time before medical therapy supplants surgery as first-line treatment for all functional tumors rather than just prolactinomas. Further research into the genetics of pituitary tumors will also contribute to understanding subtle differences within each tumor type and pave the way for the discovery of new highly specific medical treatments optimally suited for a given tumor. It will also allow us to have a better idea, at the time of the diagnosis, of which is the best initial treatment modality to pursue, based on the known history of responsiveness of the genetic subtype. Ultimately, however, it is the continued multidisciplinary approach to patient management complete with detailed imaging of the pituitary gland, a comprehensive hormonal panel, a thorough evaluation by a neurosurgeon, endocrinologist, and ophthalmologist when indicated, and full consideration for medical, surgical or radiation treatment, which will always contribute to providing the most effective care for patients with pituitary adenomas.

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HEMATOLOGY ROUND
Light Chain Myeloma

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Introduction

Plasma cell dyscrasias are plasma cell neoplasms developed as a result of malignant proliferation of a monoclonal population of plasma cells. These diseases are associated with a monoclonal protein (M protein) produced by clonal plasma cells. They include monoclonal gammopathy of undetermined significance (MGUS), isolated plasmacytoma of the bone, extramedullary plasmacytoma, smoldering myeloma, and multiple myeloma (MM). Other rare conditions of plasma cell dyscrasias include Waldenstrom's macroglobulinemia due to IgM producing plasma cells, POEMS syndrome (peripheral neuropathy, organomegaly, endocrinopathy, monoclonal plasma cell disorder, skin changes), and AL Amyloidosis (1).

Normal plasma cells produce immunoglobulins consisted of 2 heavy chains and 2 light chains (Fig 1). There are 5 different kinds of heavy chains (IgG, IgA, IgM, IgD and IgE) and 2 types of light chains (kappa and lambda). In myeloma, cancerous clonal plasma cells make the same immunoglobulins. Therefore, the myeloma can be classified by the type of the heavy and light chains produced, for instance, IgG lambda, IgG kappa, IgA lamba, IgA kappa, IgM lambda, IgM kappa, IgD lambda, etc.

In about 20 percent of myeloma, cancerous plasma cells produce only light chains, which is called "light chain myeloma". Because the light chains have small molecules, they are excreted into the urine easily and can be identified with Urine Protein Electrophoresis (UPEP) and Urine Immunofixation Electrophoresis

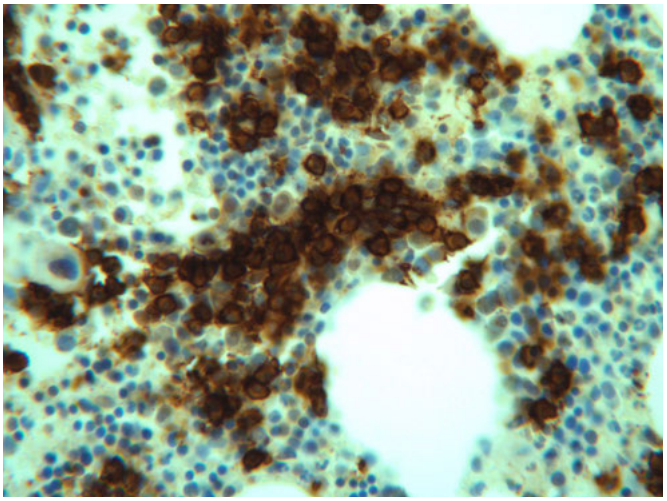

Fig 1A: H&E stain of bone marrow aspirate shows many plasma cells.

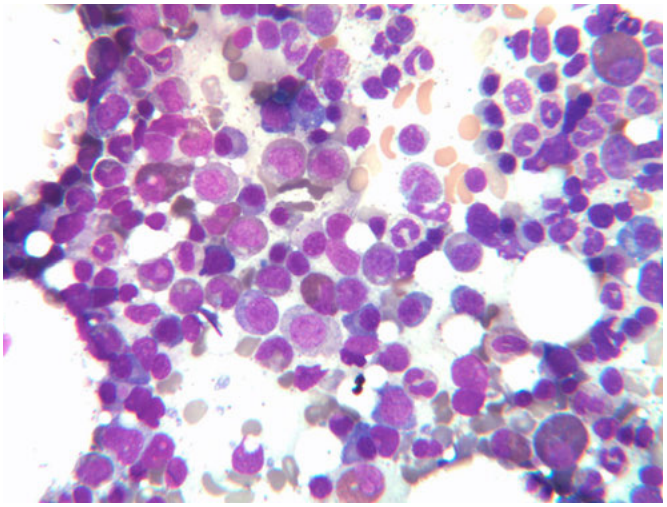

Fig 1B: CD138 stain shows areas of more dense plasma cell infiltrate

(UIFE). The light chains found in the urine is called "Bence-Jones Protein". A 24-hour urine collection is necessary to quantify the amount of light chains because Serum Protein Electrophoresis (SPEP) frequently cannot detect the light chains in the blood as lights chains are rapidly excreted into the urine without glomerular filtration due to the small molecular weight. Recently developed "Free Light Chain (FLC) Assay" can identify and quantify these light chains in the blood. Now, many hematologists are using serum FLC assay in replacement of the 24-hour UPEP (2). The light chain myeloma is classified as lambda light chain or kappa light chain myeloma.

In 2003, the International Myeloma Working Group (IMWG) established diagnostic criteria for 3 plasma cell dyscrasia conditions (3): (1) Symptomatic Myeloma; (2) Asymptomatic (Smoldering) Myeloma; (3) MGUS. Patients with Symptomatic Myeloma need immediate treatment, but those with Smoldering Myeloma and MGUS do not need immediate therapy until progressed to symptomatic myeloma. Patients with MGUS develop MM at the rate of 1% per year. But a recent research study suggested that high risk Smoldering Myeloma patients may get benefit from early treatment (4).

Diagnostic Criteria of Symptomatic Myeloma (all 3 are required):

1. Presence of an M-protein in serum and/or urine.
2. Clonal plasma cells >10 % on bone marrow biopsy (or presence of clonal plasma cells in any quantity in a biopsy from other tissue in case of plasmacytoma).

3. Evidence of end-organ damage: hypercalcemia, renal failure attributable to myeloma, anemia of hemoglobin <10 g/dL, bone lesions (lytic lesions or osteoporosis with compression fracture. An acronym of CRAB was made to represent the first 4 conditions (hyperCalcemia, Renal failure, Anemia, Bone lesions).

Diagnostic Criteria of Smoldering Myeloma:

1. Serum M protein >3 g/dL AND/OR
2. Clonal plasma cells >10% on bone marrow biopsy AND
3. NO myeloma-related organ or tissue impairment

The diagnostic criteria of MGUS include:

1. Serum M protein <3 g/dL AND
2. Clonal plasma cells <10% on bone marrow biopsy AND
3. NO myeloma-related organ or tissue impairment

Case Report: Initial Presentation

Mr. M.A is an 81 year-old man who developed anemia 2 years ago when his hemoglobin level was 9.9 g/dL, hematocrit 29%, MCV 90 fL and platelet 288 k/uL. The anemia had been gradually worsening without any obvious signs of bleeding. Esophagogastroduodenoscopy revealed chronic gastritis. About 6 months later, the hemoglobin level was 8.7 g/dL and bone marrow biopsy was done elsewhere. The pathology reported that the examined bone marrow showed 10% plasma cell involvement according to the CD138 marker study with lambda light chain restriction. Cytogenetic study was normal, but fluorescence in situ hybridization (FISH) study for plasma cell dyscrasia was not done. Serum protein electrophoresis (SPEP) did not show M-spike indicating absence of noticeable M-protein in the serum. Serum free light chains were measured: abnormally high lambda light chains at 43.5 mg/dL, normal kappa light chains at 3.56 mg/dL, and abnormal kappa/lambda ratio at 0.0818 (normal ratio: 0.26-1.65). Bone survey did not find lytic bone lesions. The serum creatinine level was slightly high at 1.8 mg/dL with a single kidney as he had right nephrectomy for early renal cell carcinoma in the remote past. Serum calcium level was normal at 9.4 mg/dL. The serum beta-2 microglobulin level was high at 4.9 mcg/mL (normal range: 0.7-1.8). Quantitative serum immunoglobulin test showed low IgG level at 628 mg/dL (normal range: 700-1600) and IgM level at 45.5 mg.dL (normal range: 60-300). As he required blood transfusion every 3-4 weeks for progressive anemia, he was referred for a second opinion and the previous hematology laboratory data were reevaluated.

Discussion with the initial presentation

Although M protein was absent in SPEP, he has abnormally high serum lambda light chains with abnormal kappa/lambda ratio, indicating proliferation of monoclonal plasma cells producing lambda light chains. The normocytic and normochromic anemia could be directly related to the plasma cell infiltration in the bone marrow because there was no obvious evidence of occult bleeding elsewhere. The pathology reported as about 10% plasma cell involvement in the bone marrow, not as >10%, which makes it difficult to diagnose MM according to the diagnostic criteria above. One may notice that the bone marrow criteria above is arbitrary

because: (1) the bone marrow biopsy sample may not represent the accurate status of the bone marrow plasma cell infiltration as plasma cells are often focally aggregated rather than diffusely infiltrated; and (2) the evaluation of the plasma cell infiltration by pathologists can be subjective as some pathologists may say 9% or others may interpret as 11% with the same specimen. In fact, approximately 4 percent of patients may have fewer than 10 percent bone marrow plasma cells since marrow involvement may be focal, rather than diffuse (5).

There are immunohistochemical biomarkers helping to distinguish cancerous myeloma cells from benign plasma cells:

1. The CD138 is an excellent marker for plasma cells for both mature and malignant plasma cells in bone marrow. The patient in this case had immunohistochemical stain with the original bone marrow biopsy specimen for CD 138 reactivity, and the pathologist estimated that about 10% of bone marrow cells were positive for CD138. However, this method has limitation as immature plasma cells of higher proliferative potential tend to be CD138 negative, meaning that some real malignant myeloma cells can be CD138 (-) while more mature plasma cells are CD138(+). Therefore, assessment by measurement of CD138 reactivity can underestimate the extent of plasma cell involvement in the bone marrow (6). Then, the "about 10%" actually could mean "at least 10% or more".

2. The CD19 is highly expressed in MGUS but not in MM. Plasma cells bearing this antigen could represent the non-neoplastic process and determination of its expression is useful for the diagnosis of MGUS (7). This patient has negative CD19.

3. The CD56 marker is also very useful as CD56 is usually positive in plasma cells of MM, whereas negative in those of MGUS (8). The phenotype analysis of the bone marrow of this patient was CD56 positive.

Therefore, as the phenotype analysis of flow cytometry of the bone marrow revealed negative CD 19 and positive CD56, the plasma cells of his bone marrow are more likely malignant rather than benign, strongly suggesting that he has MM rather than MGUS.

Because the quantitative immunoglobulin test showed low serum IgG and IgM levels, he is prone to serious infections, especially to encapsulated organisms such as Strep. pneumoniae, H.influenza and Group B streptococcus.

Follow up of the case

This patient had bone marrow biopsy and serum free light chains analysis again almost 1 year after the initial presentation: The amount of CD 138 (+) plasma cells in the bone marrow biopsy was now estimated as 15% (Fig 2). The FLC assay also showed increased serum levels of free lambda chains at 69.5 mg/dL but no change with kappa chains at 3.88 mg/dL. The serum albumin levela was normal at 3.5 gm/dL and the creatinine level at 1.8 mg/dL. The beta-2 microglobulin level went up to 5.4 mg/dL. The beta-2 microglobulin correlates with the extent of disease and tumor burden, but is not helpful in the presence of renal failure (when the creatinine level >2mg/dL) as then the test is falsely elevated.

The International Myeloma Working Group (IMEG) published the International Staging System (ISS) for myeloma in 2005 (9):

1. Stage 1: 2-microglobulin <3.5 mg/dL and albumin > 3.5 g/dL
2. Stage II: 2-microglobulin <3.5 mg/dL and albumin <3.5 g/dL; or 2-microglobulin > 3.5 mg/dL and albumin < 5.5 g/dL
3. Stage III: 2-microglobulin > 5.5 mg/dL

The ISS system used 2-microglobulin as the main prognostic factor after extensive review of myeloma patients by IMWG. Therefore, this patient has the Stage II myeloma according to the ISS. Overall median survivals for the 3 stages when the ISS system was published in

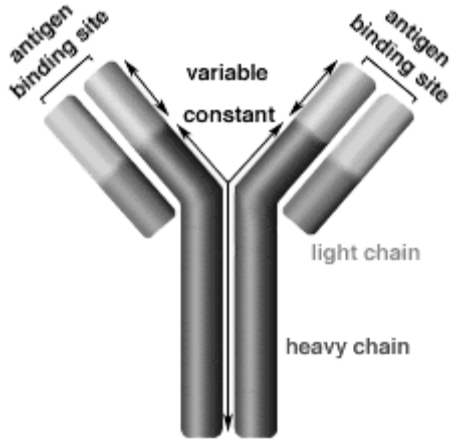

Fig 2

2005 were shown to be: Stage 1: 62 months; Stage II: 45 months; Stage III: 29 months. Because of the advent of new anti-myeloma therapy since then, this survival estimates may not be accurate.

Patients with light chain myeloma is particularly susceptible to acute and chronic renal failure. Tubular injury presumably results from the reabsorption of some of the filtered light chains into the tubular cell. Their accumulation within the cell may then interfere with lysosomal function resulting in renal failure (10). Myeloma patients also often develop cast nephropathy. Light chains precipitate in the tubules as a result of binding with Tamm-Horsfall mucoprotein (THMP, also called uromodulin), which is a protein of uncertain function that is normally secreted by cells of the thick ascending limb of the loop of Henle and that constitutes the matrix of all urinary casts (11). The binding and precipitation leads to the formation of obstructing, dense, intratubular casts in the distal and collecting tubules leading to interstitial inflammation and fibrosis. Volume depletion contributes to cast nephropathy, possibly by slowing flow within the tubules and by promoting the formation of large aggregates. Other mechanisms of renal failure in myeloma include immunoglobulin light chain (AL) amyloidosis and light chain deposition disease in which amyloid and light chains are deposited in organs, especially in the kidney. In this patient who had nephrectomy, total amount of light chains are excreted into one kidney, thus doubling the risk of nephropathy.

The genetic makeup of the myeloma cells has a significant effect on outcome. The bone marrow aspirates should always be sent at the time of diagnosis of plasma cell dyscrasia for chromosome analysis by traditional cytogentic techniques and FISH test. Up to 50% of patients with myeloma have acquired chromosomal defects. Deletion of chromosome 17 [del (17p13)] and translocations from chromosome 4 and 14 [t (4;14)] have been associated with poor prognosis with median survival of less than 2 years. Patients with translocations between chromosomes 11 and 14 [t(11;14)] are known to have standard risk (1). Other study showed that multiple gains of chromosomes (hyperdiploidy) have been associated with good prognosis. The chromosome analysis by both cytogenetic and FISH with the second bone marrow aspiration specimen of this patient showed normal study, indicating that he has neither poor nor good prognostic chromosomal changes.

Recently many combination drug therapies are developed for MM with promising result, which include bortezomib (Velcade®), thalidomide and lenalidomide (Revlimid®) used in combination with cyclophosphamide (Cytoxan®), melphalan (Alkeran®), prednisone and dexamethasone (1). Although many of those combination therapy improved response rate and disease free survival rates, they did not show clear-cut advantage in overall survival rate when compared with traditional myeloma therapy. Nevertheless, younger patients with the ages less than 70 years are eligible for autologous stem-cell transplantation which can result in the nearly complete response up to 57% (1).

He was treated with single-agent dexamethasone pulse therapy with low dose of dexamethasone in view of his advanced age and comorbidity (12). After total 4 cycles, the FLC assay was repeated and showed remarkable improvement: the serum free lambda light chains dropped to 8.22 mg/dL from 69.5 mg/dL. He no longer required blood transfusion since then. The serum creatinine level also improved to the range of 1.3-1.6 mg/dL. Elderly myeloma patients need special attention as they do not tolerate aggressive chemotherapy (12). A common saying that comes to mind is "the cure is worse than the disease".

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PLANT-BASED COMBINATION ANTI-EMETICS FOR CHEMOTHERAPY

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Introduction

Nausea and vomiting are a frequently encountered side effect of many chemotherapeutic agents. The physiological processes involved in vomiting are complex and involve the release of multiple neurotransmitters (5). Likewise, the emetic reflex arc is a highly complex and integrative system whose detailed circuitry is only partially characterized. It is also important to note that not all animals are capable of vomiting and thus full characterization of the emetic circuit has been limited.

Cisplatin is clinically effective against a variety of tumors (14) but is also one of the most emetogenic antitumor therapies currently in use (18). This side-effect of cisplatin is biphasic in nature with the initial phase persisting up to 24 hours post administration in cancer patients, followed by a delayed phase days 3-7 following cisplatin treatment (8). Cisplatin-like drugs are thought to induce vomiting mainly via release of serotonin (5-HT) and substance P (SP) in the upper gastrointestinal tract (GIT) and brainstem which may directly activate their respective corresponding local 5-HT3- and tachykinin NK1-receptors (5). Moreover, 5-HT and SP can also indirectly activate brainstem emetic loci via stimulation of NK1- and 5-HT3-receptors present on vagal afferents in the GIT whose somata are in the nodose ganglion, and whose terminals are present in the area postrema (AP), the nucleus of the solitary tract (NTS), and the dorsal motor nucleus of the vagus nerve (DMNX) (Figure 1) (5).The latter cluster of emetic nuclei is collectively described as the brainstem dorsal vagal complex (DVC). Since no single anti-emetic agent can prevent cisplatin induced vomiting (CIV), combined prophylactic therapies are almost always a necessity.

Clinical Application

Current prophylactic treatment for the prevention of cisplatin-induced vomiting includes the use of dexamethasone for both phases of CIV, plus a 5-HT3-receptor antagonist (e.g. palonosetron) for the suppression of the immediate emesis, as well as an NK1-receptor antagonist such as aprepitant for the management of the delayed phase (18).The nausea and vomiting caused by cisplatin is distressing to patients and can reduce compliance and the quality of life of cancer patients receiving such treatment (9). Even with the use of triple antiemetic regimens, 20-30% of patients can still suffer from vomiting.The goal of modern antiemetic therapy is to abolish both CIV phases in order to allow all patients to continue effective antitumor therapy.

Delta-9-tetrahydrocannabinol (9-THC) is the main psychoactive component of marijuana and has been shown to possess significant antiemetic efficacy against both phases of CIV in animals and patients (1, 5). 9-THC inhibits CIV via the stimulation of cannabinoid CB1 receptors in both the brainstem and the GIT (6, 13, 17). Although the efficacy of 9-THC to suppress acute phase CIV is less than that of 5-HT3 receptor antagonists, the latter class of antiemetics is poorly effective against

the delayed phase (7, 18). Furthermore, a combination of 9-THC and 5-HT3 receptor antagonists leads to only minor or no additional antiemetic efficacy in both animals and patients (11, 12, 19).

The transient receptor-potential vanilloid-1 receptor channel (TRPV1) is a target of the pungent component of chili peppers, capsaicin. Its ultrapotent analogue resiniferatoxin (RTX) from the plant genus Euphorbia has been used in patients for pain relief and urinary incontinence (10). RTX has also been shown to possess potent (100 μg/kg, s.c.) antiemetic properties against several centrally- and peripherally-acting emetogens, including cisplatin, in both ferrets and house musk shrews (2, 3). However, RTX not only has undesirable actions on cardiovascular and pulmonary systems (16), but any dose larger than 10 μg/kg also causes significant vomiting by itself in the house musk shrew (2). In an attempt to resolve the latter issues, investigators have used nonpungent TRPV1 agonists, such as olvanil, or synthetic hybrid agonists of CB1 and TRPV1 receptors, such as arvanil, for their antiemetic potential. However, these agents lack full antiemetic efficacy against CIV or copper sulphate-induced emesis (4, 15). Since TRPV1- and CB1-receptors are known to co-localize in the brainstem emetic nuclei (15), it is possible that a combination of nonemetic ultralow dose(s) of RTX (e.g. 1 - 5 μg/kg) with low doses of 9-THC (e.g. 0.025 – 0.5 mg/kg) may provide additive antiemetic activity without producing significant side-effects.

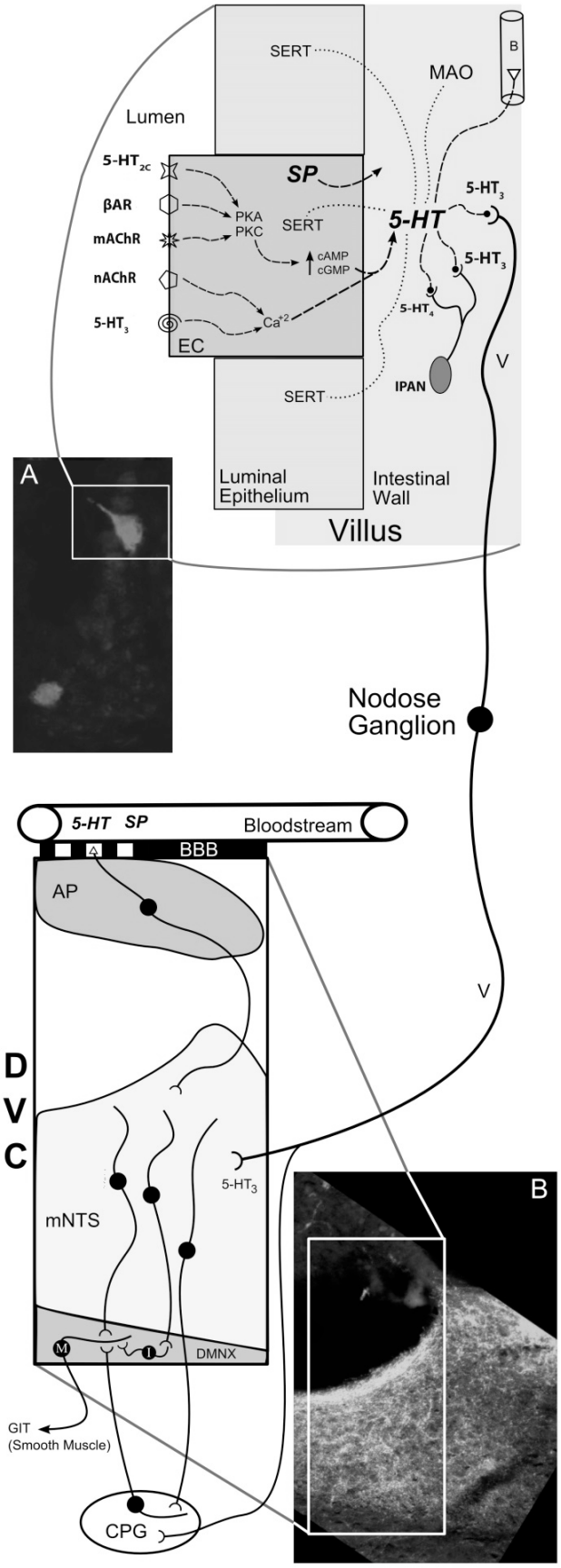
Methods and Results

We investigated this possibility in a validated animal model of emesis, the least shrew (Cryptotis parva). Our results reveal that RTX by itself caused vomiting in a bell-shaped dose-dependent manner when administered subcutaneously (s.c.) but not intraperitoneally (i.p.). 9-THC up to 10 mg/kg provides only 80% protection of least shrews from cisplatin-induced emesis in least shrews and humans. Combinations of 1 or 5 μg/kg RTX with varying doses of 9-THC completely suppressed both the frequency and the percentage of shrews vomiting with ID50 dose values 5- 50 times lower than 9-THC doses tested alone against cisplatin.

Discussion

In conclusion, our results extend previous observations that combinations of various antagonist anti-emetics are more efficacious than each antagonist tested alone, by demonstrating that combinations of sub-

Figure 1



therapeutic doses of antagonist anti-emetics such as RTX and Δ9-THC have the potential to completely abolish CIV. These findings show promise of efficacy superiority to the standard currently used triple drug regimen (Dexamethasone, a 5-HT3-receptor antagonist, and a NK1-receptor antagonist). More importantly, the antiemetic benefits are experienced at doses with low side-effect potential, providing optimism for extended patient adherence. Further studies should consider evaluating long term antiemetic efficacy of such dual agent therapy. Ultimately, the largest avoidable origin for a failed drug therapy is inadequate patient adherence owing to troublesome side effects. Therefore, we believe our findings in the least shrew would translate to an increase in patient adherence that can make the distinction between life and death.

Figure 1 (previous page)

Photomicrograph A depicts a strip of least shrew luminal epithelium (boxed area) from a villus immunolabeled for 5-HT (red) to highlight enterochromaffin cells. Enterochromaffin cells can be stimulated to release 5-HT by a variety of luminal membrane-bound receptors, ultimately leading to stimulation of various second messenger systems (dashed lines in diagram). Photomicrograph B depicts a coronal hemisection of the dorsal vagal complex (boxed area) of the least shrew, immunolabeled for SP (blue) and 5-HT (green). Vagal afferents projecting from the nodose ganglion to both the gut and brain. The area postrema neurons can access the bloodstream through the locally fenestrated blood-brain barrier, thus enabling rapid communication between the brain and gut. Upon vagal stimulation, the nucleus of the solitary tract (or serotonergic and/or tachykininergic stimulation of the area postrema) induces the emetic motor output of gastrointestinal tract smooth muscle via action on both motorneurons (M) and interneurons (I) of the dorsal motor nucleus of the vagus, while concomitant stimulation of the central pattern generator area near the nucleus ambiguus coordinates related prodromal respiratory/salivatory activity (precursors to vomiting) with the actual act of vomiting.

Abbreviations: 5-HT, serotonin; 5-HT#, serotonin receptor subtype; AP, area postrema; AR, beta-adrenergic receptor; B, blood vessel; BBB, blood-brain barrier; CPG, central pattern generator area; DMNX, dorsal motor nucleus of the vagus; DVC, dorsal vagal complex; EC, enterochromaffin cell; GIT, gastrointestinal tract; IPAN, intrinsic primary afferent neuron; mAChR, muscarinic cholinergic receptor; MAO, monoamine oxidase; mNTS, medial subnucleus, nucleus of the solitary tract; nAChR, nicotinic cholinergic receptor; PKA/PKC, protein kinase A/C; SERT, serotonin reuptake transporter; V, vagal afferent nerve fiber.

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COLLABORATIONS IN HEALTH EDUCATION FOR LOW-RESOURCE REGIONS

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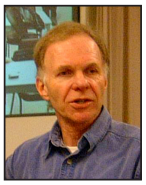

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Introduction

"Where you live should not determine if you live." Who could not agree with that? Health care should be equitable in rich and poor countries alike, but of course it isn't so. Unequal budgets, resources and education result in huge disparities and often determine who lives and who does not.

In underserved regions, you are four times more likely to die from non-communicable diseases, such as cancer, respiratory diseases and diabetes. Women living in developing countries are nearly 300 times more likely to die from complications during pregnancy and childbirth than women living in developed countries. Babies are less likely to see their fifth birthday—the under-five mortality rate is eight times higher in Africa than in Europe. People entering their sixties in low-income countries have already passed their life expectancy, where people in high-income countries live nearly 20 years longer.2

Medical staffing is unequal. In underserved regions, there are fewer physicians per capita and vastly fewer specialists, and this weighs heavily on primary care physicians (PCPs). And PCPs might do better, but continuing medical education opportunities, abundant in wealthy countries, are all but absent in poor countries. Availability of journals is limited, access to conferences is restricted, online opportunities for information and training are impeded by poor Internet connections and limited funds to pay for connections.

The Primary Health Care movement, started by the World Health Organization (WHO) in 1978, sought to provide an avenue for developing countries to acquire universal access to health services and to improve the quality of health by providing preventive, curative and rehabilitative services. Many factors, however, undermined the quality and efficiency of primary healthcare services, including poor provider skills, directly related to ongoing education and the availability of reliable, current information. In order to improve primary care services, a number of approaches are used, one of which is training to improve medical knowledge and clinical skills and doctor-patient interaction.

Augmenting the efforts of clinical professionals, community health workers (CHWs) have, over the years, become part of the expansion of basic health services in developing countries.7 Inevitably some of these CHWs operate in isolation in remote rural areas where they face problems communicating with outside health officials.8 With inadequate base training, CHWs are less likely to be effective. The WHO and many Member States are advocating short training courses for CHWs with the

aim to equip them with the skills necessary to deliver specific interventions. 5

One essential strategy to improve health outcomes in low-income regions is the cultivation of a relationship that values the patient as a partner in his or her own care and by providing patients with education and training. Thus, in the new paradigm of health care, there is a strong emphasis on collaboration and teamwork between medical professionals, healthcare workers and patients. Inherent in the creation of these robust partnerships is the availability of accurate information and reliable training programs for all players.

An expanded view of the patient as an active participant in the healthcare process is particularly important in under-resourced regions. But it is evident that patients and people in remote areas face a lack of health information as do their medical professionals. Grassroots audiences in upper-income countries can easily consult the Internet for basic information, and while this can be a blessing and a curse, with proper cautions about source credibility, people can access a treasure trove of educational resources. People with insurance and access to health systems can get information from their physicians, nurses and others in the provider system.

Grassroots populations in underserved regions have little of this. They are much less likely to have computers or Internet access, and even if the Internet were available, for most people it isn't affordable. With fewer doctors per capita, they are less likely to have access to the professional medical community, and so that isn't a viable source of information. Libraries are scarce and where they exist, they are unlikely to stock up-to-date, health-related material.

So, the deck is heavily stacked against the people and their medical professionals in low-income countries. Many people accept that fate alone determines who gets sick and who gets well. How would they learn otherwise? The inequality of health knowledge is evident, it's dangerous and it's wrong. Individuals and communities that understand even the basics of good health can make vast improvements in health outcomes.

An information technology-based model

The root of health knowledge inequality is almost always economic inequality, a global problem about which we can do little. We can, however, address the information and education opportunity issue directly. Specifically, we can gather the information from the high-income countries, package it and deliver it to people in low-income countries. Driving the point more directly, we can tap the expertise of medical professionals, such as readers of this article, to share with people who don't have access to medical or health information.

WiRED International, a volunteer-driven, non-profit organization has been delivering medical and health information to war-affected and low-income regions since 1997. All our educational programs are technology-based. Starting in the 1990s, we stored programs on floppy disks and CD-ROMS, and today we rely on the Internet and flash drives. With this technology, you can put hundreds of training programs in someone's pocket, take them beyond the grid, and run them on portable laptops and projectors powered, if you wish, by a solar-charged battery the size of a paperback.

Several years ago, WiRED developed the Center for the Development and Distribution of Health Education Programs. The virtual Center draws intellectual content and resources from regions of abundance, processes it for new audiences and distributes that information to regions of scarcity. Sometimes both regions of abundance and scarcity are within the same country, but not very often.

WiRED serves as a facilitator: We work closely with medical and health professionals to cultivate the educational material; WiRED's team of technology experts, medical editors, imagers and writers then prepare the interactive programs. We distribute these resources to areas where they're needed—through many channels including hospitals and clinics, other NGOs, our own educational facilities and the Internet. We're now beginning a program with Caritas to bring these health education programs to many additional communities. For instance, in spring 2014, we completed a training module on Ebola—in English and French—and within an hour, Caritas had distributed it throughout East Africa, where Médecins Sans Frontières said the disease was "out of control." Most programs are designed for grassroots audiences; increasingly we are building tools for medical professionals and CHWs.

Let's go back to the source of information: How do we obtain the intellectual content? We rely on three general approaches. First, our in-house medical writers propose topics based on their ongoing research of global health conditions. Second, we field requests from physicians, health ministries, other non-governmental organizations

(NGOs) and universities for assistance with a topic of importance in a given region. In response to this request, WiRED identifies medical experts who prepare the material. Finally, we invite physicians, nurses and health educators with a particular medical expertise to propose topics for which they would provide content. If a review panel determines the topic is relevant to audiences in low-income regions, we will work to create the program with the experts who proposed it.

Consider three examples. Two years ago, Australian pediatricians with an expertise in rheumatic heart disease (RHD), proposed a set of modules to train nurses and first-line health workers how to acquire and interpret echocardiograms to screen for RHD. Because of the increasing availability of portable ultrasound equipment, the timing for such an undertaking was perfect. The pediatricians teamed up with a third physician from the Royal Berkshire Hospital in the United Kingdom, and they, together with input from WiRED's medical editors and IT experts, worked for 18 months. The modules were peer reviewed, and the finished package was released at the World Congress of Cardiology in spring 2014. The modules were then made available world-wide through WiRED's resources so that nurses and CHWs can study echocardiographic procedures in remote regions. We are also preparing an online and portable video bank to allow professionals studying these modules to practice and test their skills.

This case offers a good example of the concept: It drew intellectual content and resources from regions of abundance, processed the information for new audiences and distributed the material to regions of scarcity.

This next example has several interesting features. A U.S. physician from Southern California, working in Hunan Province, China, was looking for training material on hypertension. WiRED had just updated its hypertension module, which the physician thought would be useful, but the material was in English and his audience read only Mandarin. Responding to the request for a translation, within two weeks, WiRED prepared a Mandarin version of the module.

The same physician, who was training Chinese rural doctors to screen for infant heart murmur, asked if WiRED had a module with recordings of infant heart sounds. We did not, so the American physician, a pediatric cardiologist, proposed to write one. We accepted his proposal and collaborated on the production of a training module that describes what to listen for in the infant heart and provides ample examples of normal and abnormal heart sounds. The module was written in English and translated into Mandarin. We have made the English-language version available globally to help medical professionals anywhere screen for infant heart murmur. Here we see that a need arising in the field, then addressed by a medical expert collaborating with WiRED's technicians, created a tool that now benefits physicians working anywhere in the world.

The last example takes place in the fall of 2013 when the media suddenly filled with reports of a polio outbreak in Syria and surrounding countries. Because polio had been viewed by most experts as all but eradicated, in recent years it fell from view. Many physicians, nurses and CHWs, never having seen or studied the illness, were unfamiliar with polio's signs and treatments. WiRED's contacts in the Middle East asked if we could quickly assemble material to update medical staffs working in the region. Drawing mostly from Centers for Disease Control and Prevention reports, our writers immediately set out to create a "Rapid Response" module. Within three days, the module was written, edited and peer reviewed; and in one more day it was packaged as an interactive module and released online in WiRED's Community Health Education e-library—in English and Arabic. We also distributed the modules as portable files that people could download and take on their laptops and thumb drives into the field, where Internet access is difficult. Caritas, a global partner, also distributed both language versions to all its clinics and hospitals throughout the Middle East.

These examples demonstrate that while the identification of topics and the sources of intellectual content arise in several ways, in all cases there is movement of educational material from where it is plentiful to where it is scarce. Doctors who know about the echocardiographic diagnosis of RHD or about the sounds of heart murmur or the plague of polio or about hundreds of other medical and health conditions freely offer their expertise to assist their colleagues and grassroots communities thousands of miles away.

It is important to note that in this entire process, very little money changes hands. Writers, for the most part, are volunteers, donating their expertise to this community effort. Medical editors, peer reviewers, coordinators, computer programmers and most others in the production system volunteer their time or work for minimal wages provided through small grants and individual donations. WiRED's administrators, board

and field workers are volunteers. Through a network of partnerships, usually with organizations whose mission focuses on health care and health training, programs are disseminated by people who volunteer or who are modestly paid.

The role of patients in patient care—teaching grassroots communities

So far we have emphasized programs for medical professionals, but much of our work is with grassroots communities, where we feel we can make a significant impact on community health. Poor patient to physician ratios and a scarcity of CHWs and other trained medial staff leave huge portions of these populations without the level of medical care seen in upper-income countries. In some places we work, professional health care simply doesn't exist.

So, what can we do under such austere conditions? We believe that basic training in prevention, recognition of signs and symptoms and a general knowledge of healthy practices can go a long way to improve health outcomes in low-income regions. As we described earlier, many community health experts at the WHO and elsewhere now view patients and people off the grid as essential elements in the health collaboration.

Take a simple example. Dental problems plague people everywhere, but especially in low-income countries, with few dentists, a simple problem can lead to serious outcomes. Cavities and periodontal diseases are most prominent, but many low-income communities face noma, gingivitis and cancers that, in many instances, can be prevented. Prevention is the key for many dental issues.

Clearly, if people brushed their teeth regularly, they would head off many of the dental problems faced in low-income regions. Yes, brushes aren't always available, floss is rare, toothpaste can be costly, but one of the biggest problems is ignorance about teeth cleaning.

Another problem is the consumption of high-sugar foods, which have displaced healthier dietary options. In villages on the Amazon, where we have set up several health training programs, people once ate peanuts—the entire peanut, shell and all. Mechanical action of the shell would clean the teeth; the few sugars in the peanut were not a problem. Within the past decade, candy and soda have become available, even in many remote locations, and these sweets have pushed peanuts off the diet. Implications for dental health are twofold: first, the sugar-loaded treats induce tooth decay. Second, eating candy has displaced the healthy, teeth-cleaning practice of chewing peanuts.

We found that most people in these communities simply don't know about the importance of brushing and they are unaware of the dental hazards associated with sweets. With the input of dentists, WiRED has developed training modules that explain the impact of brushing, flossing and a good diet on dental health. We show people how to brush, how to floss, and explain why they should avoid sweets.

Some people argue that providing the knowledge but not the means of putting it to use—teaching about brushing but not supplying brushes, for example—is a waste of time. We don't agree. People may not be able to implement all the suggestions, and they may not have access to all the tools, but basic information helps them make good choices when opportunities arise. And people can improvise. We saw people using make-shift brushes from a tropical plant and salt instead of toothpaste. They flossed with thread. We don't know if people have avoided sweets and returned to peanuts, but we plan to research this in the next year. The point is that people cannot make good choices without good information and education about healthful practices. This program is about giving them a chance by offering them information.

Dental care is a good example, but WiRED's programs go well beyond that. We offer programs on more than 300 topics—on non-communicable and infectious diseases, community health issues, such as sanitation and clean water, pregnancy, women's health and postpartum care. Modules on cholera, dengue, malaria, diabetes, hypertension, heart disease, cancer and more offer ranging topics of global interest.

Our aim is to elevate the level of health knowledge within communities; our dream is to reach a threshold of knowledge where entire communities see prevention practices as the norm, where people are sufficiently informed to support each other on matters of good health. We see it as akin to herd immunity, where vaccinating a sufficient number of people protects the entire community. Educating a sufficient number of people about healthy practices, sign and symptom recognition and likely treatments of common illnesses can, we believe, elevate the health of the entire community.

Creating the programs, in brief

The intellectual content provided by physicians and other medical experts is the critical start of the production process. Medical editors pore over the material, then imagers select appropriate photos, diagrams and artwork to illustrate the concepts and to hold audience interest. With the text and images in place, we submit the piece for peer review and comment. At this point, the piece may return to the author for additional work, or at the reviewers' recommendation, it moves to the next step, which is to create the interactive modules. Finally, the computer-delivered module is reviewed one additional time, then placed in the Community Health Education e-library and distributed globally.

Many modules are translated for use in non-English-speaking regions. WiRED involves volunteer translators, including Translators without Borders. After the text is translated, the material is built into the interactive formats.

Delivering the educational programs

The last step is delivering the educational programs into the hands of medical professionals and grassroots audiences in low-income regions. These populations are notoriously difficult to reach. As we outlined earlier, they have limited funds, restricted communications and, to one degree or another, minimal contact with outside groups. Of course, if none of these restrictions existed, there would be little need for our work.

All computer-based programs are distributed in two ways. The most efficient is via the Internet. Although the Internet reach is growing rapidly, 65 percent of the world's population still has no access to it. This percentage is highest in Africa, with 85 percent off the grid, ranging from an estimated 99 percent in the Democratic Republic of Congo to 50 percent in Morocco. 17 In all places, access points are generally limited to urban areas. In time, emerging 3G and 4G systems are expected to expand Internet access considerably, but for now this nascent technology is not widely available in many developing regions. Even where it is available, it often isn't affordable to isolated people.

Medical professionals in cities generally have ample Internet access, but not so their rural counterparts or most grassroots audiences. For that large and isolated group, we rely on a program with three elements: (1) portable storage media, (2) Internet update portals and (3) partnerships with groups on the ground.

1. The entire Community Health Education e-library is designed to be transported on a thumb drive (flash drive), laptop hard drive or CD rom. We prepare the drives at WiRED's centers and ship them, usually via post or send them with partner organizations. Given that our aim is to make this material as widely available as possible, we encourage people to share the contents freely; they can download the programs on other laptops, copy the drives, burn new CDs. Wide and unrestricted distribution is encouraged because broad use is the key.

2. WiRED adds about one new or updated program per week. The problem with e-libraries on thumb drives is that they are frozen in time. Moreover, the Rapid Response modules, noted earlier, have greatest impact when delivered quickly to affected regions.

   To allow immediate updates, our technicians have created the WiRED "Filling Station," where people can sync their e-libraries online from anywhere in the world. Yes, people need an Internet connection, but people visiting a city can update their collection, or someone visiting a village off the grid can bring in an updated e-library.

3. Portable storage media without computers are useless, and that's where partners come in. WiRED has formed relationships with other NGOs, clinics, hospitals and organizations to help deliver the information. We provide training for people who present group sessions, and we deliver projectors and sometimes laptops with which they can display the interactive health training material. Organizers call meetings for pregnant women, people with diabetes, heart disease or hypertension. In a cholera outbreak, they will call town meetings to teach people how to deal with the illness and how to avoid contracting it. They will call a meeting to teach people how to obtain potable water using biosand filters, SODIS, and other techniques; and how oral rehydration therapy can save the life of a child with diarrhea. They go to schools to discuss hygiene, dental care and HIV/AIDS.

Partners are multipliers. Community Health Education e-libraries are easily copied and distributed, then partner organizations can reach hundreds or thousands of people with community outreach sessions. The relationship thus

helps disseminate the information while supporting the partners' mission for community health education.

Thoughts about reaching frontline health workers

A number of medical and health education organizations are working to even up the asymmetrical knowledge of health issues between rich and poor countries, and each faces the economic and resource disparity that has created the inequality. The WHO's heroic HINARI program, in operation for more than a decade, has made strides in providing medical practitioners free access to professional journals in the most disadvantaged regions. Similar materials are sometimes distributed on CD-ROMs, as they are often more accessible than the Internet. Decision support systems have also been proposed to help physicians in their daily tasks, as well as printed resources such as Blue Trunk libraries, or accessing medical information in remote areas using cell phones and smart phones. Universities and a number of NGOs offer health education programs, each approaching the assignment with different strategies.

Yet most of those approaches, although usually well accepted, mainly address the needs of physicians, nurses and healthcare workers in urban medical centres, but do not meet the information needs of frontline healthcare providers and community members in low resource settings. For many communities in developing regions, informal medical practitioners like traditional healers are the only available or affordable option for primary medical treatment. The technical and focused information relevant for urban-based physicians is unusable for both traditional healers and grassroots communities. Moreover, community-based resources often lack a reading culture relying on oral traditions for the transmission of knowledge.

We recognize the critical role of the informal traditional healer network in thousands of underserved communities and attempt to adapt our programs to support them with accurate and appropriate training. Nearly a decade ago, in many parts of Kenya, traditional healers formed clubs at WiRED Community Health Education Centers, where they carefully studied programs on HIV/AIDS. As a result, the traditional healers integrated science into their daily work on HIV prevention and patient care. The step-wise training programs, mediated by staff members, rendered the material accessible, believable and effective in changing how the healers approached HIV/AIDS and how grassroots communities responded to the epidemic.

Final thoughts

As we stated above, a number of organizations are attempting to fill the gap, balance the scales, decrease the asymmetry, call it what you like. The problems are large, the barriers huge and the scope of the shortfalls are breathtaking. There are no silver bullets, no simple answers to train medical professionals and school the grassroots in low-resource regions who suffer from a lack of health knowledge.

WiRED has adopted an approach that invites the input of experts who donate their time and skills to create educational programs that will help their unseen colleagues thousands of miles away. We also rely on these experts to help develop training tools to allow isolated people to join with their doctors and nurses and CHWs in a partnership to improve their own health and the health of their community. We love the idea of collaboration and teamwork among physicians, nurses, health workers and patients; and we strive to create a simple system that itself is a collaboration of medical and IT experts, writers and editors, administrators and people on the ground to carry the finished programs the last mile into the villages and towns in great need of health knowledge.

WiRED invites inquiries about this program and offers of intellectual contributions to the development of educational programs. Contact Gary Selnow (gary@wiredinternational.org).

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