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WMJ

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The Practice of Medicine *Past & Present*

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Mona Hanna-Attisha, MD, MPH, FAAP

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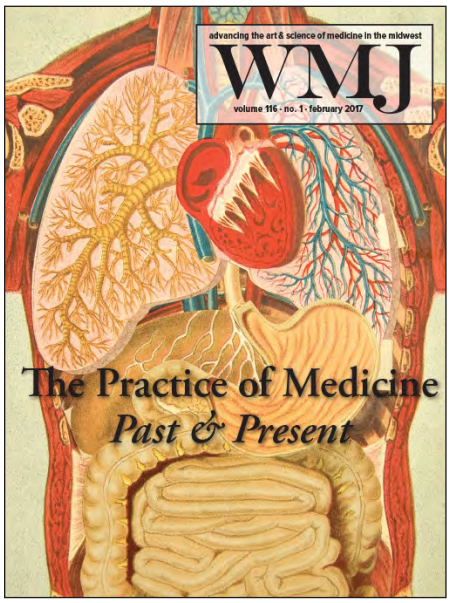

COVER THEME
The Practice of Medicine: Past and Present

In this issue of *WMJ*, author H.P. Greeley, MD, describes the changes occurring in medicine and emphasizes the importance of physician collaboration and cooperation in caring for a community. Remarkably, this essay—reprinted in its entirety—was first published in *WMJ* 100 years ago yet remains an informed commentary on the practice of medicine, both then and now.

Cover design by Kendi Parvin

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WMJ

EDITORIAL

ORIGINAL RESEARCH

REVIEW ARTICLE

The mission of *WMJ* is to provide a vehicle for professional communication and continuing education for Midwest physicians and other health professionals. *WMJ* is published by the Wisconsin Medical Society.

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CASE REPORTS

BRIEF REPORT

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Obesity Often Overstated But Hardly Understood

To the Editor:

In the November issue of *WMJ*, Dr Frey touched upon the problem of clinicians having condescending attitudes towards obese individuals.[1] However, this sociocultural aspect of obesity is often overstated but hardly understood. How can we effectively reflect upon our own biases when we are part of the society that perpetuates certain pervasive ideas about obesity and about the individuals who are categorized as being obese?

Weight stigma is an important driver of obesity because overweight individuals frequently are stereotyped as lazy, noncompliant, sloppy, undisciplined, or unintelligent.[2,3] These negative representations have lasting mental, physical, and social consequences, which drive health disparities. Mental health consequences include depression, low self-esteem, and anxiety.[4] These outcomes, combined with social exclusion and rejection, may induce behaviors and pathophysiological mechanisms favoring weight gain and increased appetite.[2] Studies have shown that bias, however unintentional, from health care providers can negatively affect the quality of health care for obese individuals.[3,4] For instance, embarrassment about being weighed, feelings of perceived disrespect from clinicians, and consequent breakdown in communication between patients and their providers create barriers to health care access and utilization.[2,3]

Weight stigma exist beyond health care settings, such as the workplace, schools, and in mass media.[2] Clinicians can better examine their own attitudes and biases when they understand the pervasiveness of weight stigma in our society as well as certain societal practices and negative consequences it produces. In addition to focusing on high-risk groups, we also need to deal with the drivers of obesity at the population level. To do so, Puhl and Heuer suggest incorporating antistigma messages into obesity campaigns and coordinating policies and legislation to facilitate health-promoting behaviors and to discourage weight-based discrimination as a society.[2] Therefore, weight stigma should be considered in conjunction with implementing interventions that aim to prevent or improve the rising incidence of obesity. To this end, clinicians also can empower their patients by utilizing health-focused metrics such as patients' progress in physical self-efficacy and attainment of health goals.

Stigma against obese individuals perpetuates negative health outcomes on multiple levels and can prevent patients from utilizing or accessing the care and resources that they might need.

If we can disrupt the social, economic, cultural, and structural norms that perpetuate stigma against obese individuals, we can make interventions more effective and be one step closer to preventing future generations from becoming vulnerable to the same conditions and outcomes.

—Sun Young Jeong, Medical College of Wisconsin

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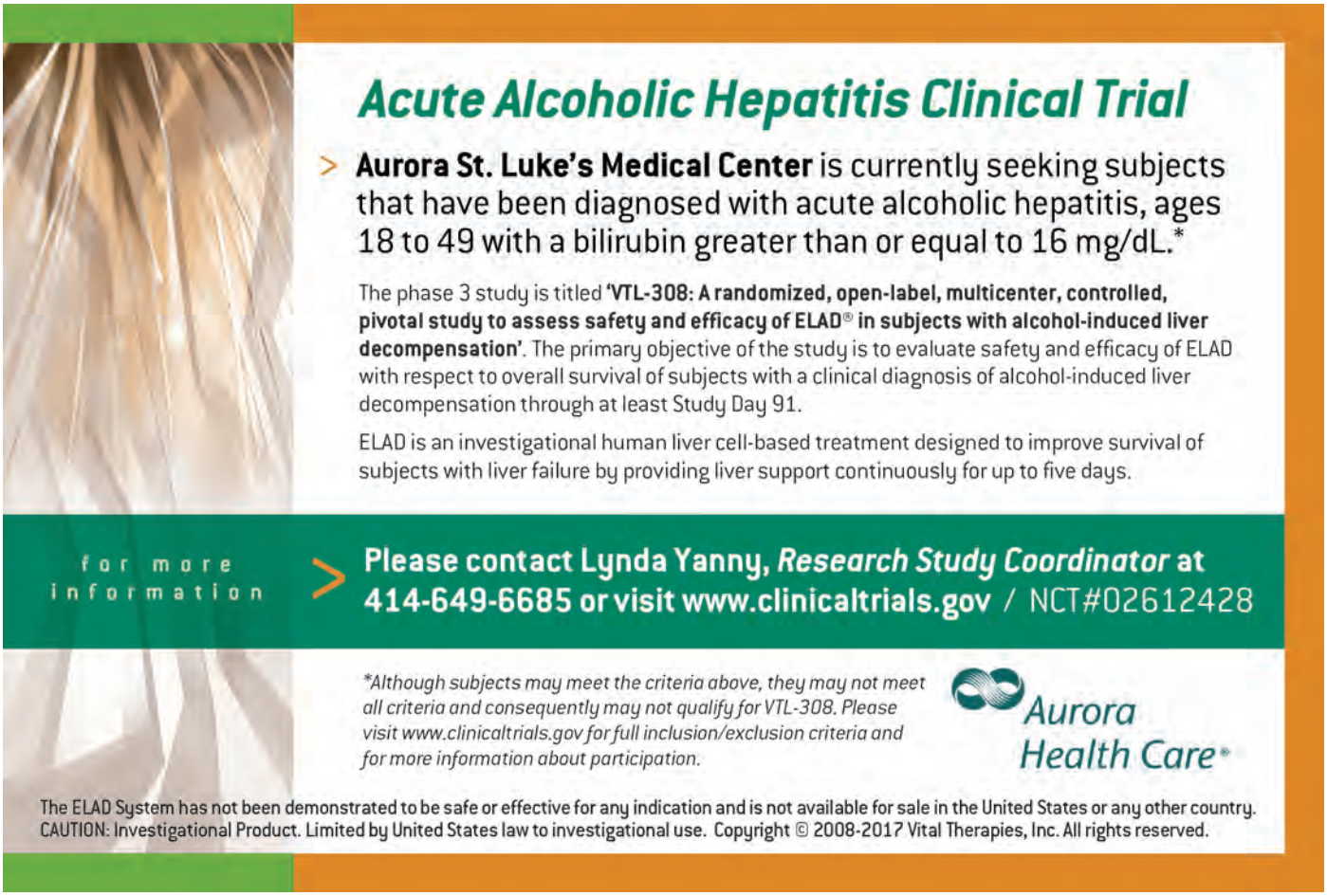

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The Physician: Past and Present

Editor's note: The following original article by H.P. Greeley, MD, of Waukesha, was first published WMJ, *in Volume 16, No. 1, p. 1-5, June 1917*

Professions as well as commercial undertakings should pause every so often for "stock taking." That means in medicine to analyze conditions and standards and see whether there is need for change or whether changes which have taken place are steps in the right direction.

Progress in science needs careful watching and there should be a "clearing house" in all lines of our work. Scientific medicine has in many phases changed the whole aspect of medical practice. The professional standards and conditions in the large cities are somewhat different from those in the country, owing to dense population and the development of specialism. City standards, however, are not without a very powerful influence on country practice, especially in those suburban towns which are easily within reach of the cities.

In the cities one often hears such questions and laments as these: What has become of the general practitioner? Is he extinct? Has his place been completely usurped by the specialist? And from those who do not approve of specialism: Has the Medical Profession deteriorated? Is it callous and commercial?

In answering these questions we must have clearly in mind the position occupied by the old time general practitioner.

Balzac has given us in the figure of "Le Medicin de Campagne" a superlative example of the general practitioner, a man who was comforter and healer of the sick, moral teacher and magistrate, the Guiding Genius of the community in which he lived. Monsieur Benassis is an ideal which every young practitioner may hold up before himself. It is surprising to me that "Le Medicin de Campagne" has not been included in those selections of works recommended to young physicians, together with the more philosophical, but less interesting "Religio Medici," the inspiring Essays of Sir. Wm. Osler, the fascinating biographies of Pasteur, Lord Lister, Marion Sims, Trousseau, and a host of others. Monsieur Benassis is not one of the great physicians of medical history but he typifies the lives of thousands of great men, who as physicians have died "unwept, unhonored and unsung" except by the few whose lives they have made worth living.

In order to determine why this type of physician is becoming extinct, let us examine into the causes for his coming into existence. It may be then that his disappearance will explain itself. In the first place, what were the conditions which surrounded the general practitioner a generation or so ago and in what respect have they changed? What was his training?

> We can clearly see, then why physicians of a generation ago were different from what they are today. At that time the medical profession to the wise and conscientious practitioner was truly an art and not a science. The efficiency of a physician depended on the extent of his experience, the accuracy and insight of his observations and the application of experience to practice...Preventive medicine was undiscovered territory.

In 1860 there were 37 medical schools in the United States, only 16 of which had any hospital facilities. Up to 1871, the training the in best schools consisted in two courses of lectures, or two terms of study of a maximum of 16 weeks each, and in addition to this an apprenticeship with a registered practitioner covering a period of three years. The latter was of course the most valuable part of his education and at the same time most elastic and uncertain as it depended entirely upon one man, whose inclination or whose fitness to teach might have varied from 1 to 100 percent. In 1871 the Medical Department of Harvard University

announced a radical change in its curriculum which brought its standard up to that of the continental schools. The change consisted in making didactic teaching continue throughout the greater part of three years. As announced it consisted in "lectures, clinical teaching, recitations, and practical exercises." Dissection had previously been the only practical work carried on by the student. Laboratories in any sense of the word as now understood were nonexistent. N.S. Davis in his history of medicine in the United States writes in 1855: "There are probably thirty to forty thousand practitioners of medicine in the United States claiming to belong to the regular profession. Of those residing in the Eastern and Middle States by far the larger proportion have regularly studied three years, attended courses of lectures and obtained a diploma from some medical college." In the South he placed the figures at less than two-thirds and in the West scarcely one-half.

Up to 1850, the highest percentage of students graduating from recognized Medical Schools, was 25 percent of the entering class. In 1872, courses in Physiology, Medical Chemistry, Pathological Anatomy and Surgery were offered at Harvard to graduates. It is evident however, from the discontinuance of this practice that there was no real need felt among physicians that they study these newly developing branches of medical science. Aside from the physician's training there were other factors which strongly contrast with conditions of today. The more even distribution of population and physicians between city and country made competition less keen. Hospitals were few and little used except by the very poor. The people as a whole were not educated to their value as institutions for treatment of disease. They were regarded as the last resort, the final resting place, an "undiscovered country from whose bourne no traveler returns."

We can clearly see, then why physicians of a generation ago were different from what they are today. At that time the medical profession to the wise and conscientious practitioner was truly an art and not a science. The efficiency of a physician depended on the extent of his experience, the accuracy and insight of his observations and the application of experience to practice. Scientific methods of study and the knowledge of the nature of infectious diseases and their control was an unopened book. Preventive medicine was undiscovered territory.

It is not to be supposed, however, that the good old general practitioner was a mediocre physician. On the contrary, according to his lights he was a better doctor than many today and a vastly better man, in spite of the tremendous gain in knowledge and in training since his time. Though his scientific knowledge must be regarded today as meager in the extreme, his experience, his keenness of observation of clinical detail and his broad humanity were unsurpassed. He studied men and women, not organs and organisms. He won a reputation for disinterested self-sacrifice and kindliness on which the faith of the community still rests. With all his belief in the pharmacopeia, he was wise enough to know that his chief weapons against disease were rarely drugs and other tangible therapeutic agents. He knew that the personal elements of sympathy, cheerfulness and encouragement, together with the common sense of good food and rest did more in contributing to the recovery of his patients than "blood-letting, purging, and packing."

He relied on Drs. Diet, Quiet and Merryman. In the light of those facts it is not otherwise than natural that one side of his nature developed more than another. His practice was his school, in which he was continually learning. Life was his laboratory. The natural result was one of the noblest works of God, a physician whose human kindliness was his most glorious attribute, of whose passing the world may well say, "Oh, the difference to me."

It is not to be supposed, however, that the good old general practitioner was a mediocre physician... Though his scientific knowledge must be regarded today as meager in the extreme, his experience, his keenness of observation of clinical detail and his broad humanity were unsurpassed. He studied men and women, not organs and organisms.

In our reminiscent lament over the passing of metamorphosis of the general practitioner there is another thing we must remember. As Lowell puts it:

"We're curus critters. Now ain't jes' the minute
That ever fits us while we're in it:
Long es t'was future, t'would be perfect bliss
Soon es it's past, thet time's wuth ten 'o thus."

The old time practitioner has not lost prestige in the passage of time.

There have been revolutionary changes in medicine and all other walks of life in the last half century. Medicine has partly conformed and followed suit and partly changed within itself, but has not separated itself widely from the current of progress. In the matter of training, which of course is secondary to the increase of knowledge, the changes have been most startling. Premedical work in science and modern languages equivalent to two collegiate years is required for entrance into the recognized schools of medicine, which follow the four years of most exacting and concentrated training in the fundamental medical sciences and in the clinical and special branches which include 10 distinct specialties. The apprenticeship with a physician has given place to one or two years' work as a hospital interne, training which up to the present time has been optional but in several states is already required. Medical schools

now graduate over 80 percent of their matriculants in contrast to 25 percent of their early period.

Even after this training, the men of promise are urged to spend still more years in special lines of research. The education which is demanded of the conscientious student of medicine flies in the face of every precept of hygiene and preventive medicine. He has practically no time for relaxation or healthy diversion of exercise. He runs a grueling gauntlet, and if he survives it is the survival of the fittest or more often the survival of a men who are no longer "fit." The physician demands made upon many hospital internes are a shame upon the profession. Complete brain and body fog has become known as "Home Officer's Disease."

Aside from this strenuous training, the graduate faces now-a-days a very different situation when he gets into practice. Competition is very keen. This is due to several factors: The shifting of the population and increase in urban physicians; the huge development of large municipal and charitable hospitals, which are no longer looked upon as undesirable places for treatment, and which remove from the hands of private physicians large numbers of patients. The growth of the specialties is another potent factor in changing conditions, as will be explained later. The development of surgery which the possibility of bringing immediate relief to patients suffering from the so-called surgical emergencies throws an added responsibility on the shoulders of the general practitioner who is not trained to this work. In the old days they were among the inevitably fatal conditions. Now-a-days the physician who does not recognize them and get immediate surgical assistance is "tried and found wanting." The general practitioner of today is a health officer as well as physician. Medicine is not standing still. Its rapid advanced keeps the practitioner keenly alive today, for what is good for one disease today is obsolete tomorrow.

Standards and conditions of practice have completely changed in almost every instance. Where 30 years ago we spoke of cure, we now speak of prevention.

Fifty years ago students of medicine learned from those whose experience had been longest, now, post-graduate study has become to be a practical necessity for all the older practitioners go back and are taught by those 10 to 15 years their juniors.

Medical practice in the cities has thus overshot the mark. In the country no such exaggeration of the science of medicine has occurred. In fact, the science of medicine, regretfully, has not penetrated the country. What the city needs is more humanity and what the country needs is more science. The general public is beginning to recognize the necessity of this and the physician who devotes some of his time every year or two to post-graduate work is beginning to have more respect than the possessor of a long gray beard which no longer carries with it the confidence it once did. To be sure, post-graduate work of a certain type is not to be regarded as a modern invention and advantage. Not only are the public beginning to be desirous that all practitioners keep abreast of the times but they are becoming equally particular what type of post-graduate work their physicians undertake, and here it may be well to digress a few moments to describe the once popular method of post-graduate study no longer desirable or possible.

We all know the enthusiasm with which American physicians have always sought the European clinics of Berlin and Vienna. Hundreds of physicians have each year in the past flocked thither. They stayed varying lengths of time but generally were content with a few weeks or two or three months at the most. To the average layman such study in Europe used to cast a halo of superiority about the physician possessing it. It was a matter of common parlance to say, "Dr. So and So, yes, he has studied abroad in Vienna." In fact most physicians in this country that did serious work and who couldn't go abroad for study looked upon Berlin or Vienna as their Carcasonne. If they never went abroad, this fact remained a source of lasting regret or constant longing. Physicians often made great sacrifices in order to visit the foreign clinics.

Many of them were uncritical and easily persuaded of the tremendous advantages of this work. Some were frankly doing it just for a good time and for the advertisement which they knew such a "vacation" would bring them on their return. But I am convinced that there was an ever increasing number of physicians who went with all enthusiasm and expectation and who came back disappointed and disillusioned about foreign study. This in no way is a reflection on the medical profession in Germany for they supplied the demand of the American physician and gave him what he wanted, neither does this statement apply to those who spent a year or more in serious work in foreign clinics. But they are relatively few. They generally remained at one clinic and did not put in an appearance at the large cities. The average physician received his medical pabulum as rapidly and in as large does as he could pay for it.

Go to any lunch counter at home and you may see a similar sight. All the crudities and mannerisms for which we are caricatured are in evidence. From the method of handling table utensils to the manner of stoking food and the peculiarities of our national tastes. In Vienna you could have seen the same phenomena at the medical lunch counter. Some were there for one month and they gorge themselves eating much and digesting little. Others were there for the side shows and the beer and took only food enough to get their certificate, which the University of Vienna issued to anyone who could pay the price of a course, whether he attended or not. Generally courses were served up in German and so rapidly served that the average American lost the meat and only got the names of the courses. Sometimes they attempted to furnish English dishes and then the job was generally botched. The German language alone is an all sufficient argument against post-graduate study for the average American physician. All the teaching is didactic and this, again, condemns it from the point of view of serious work in modern medicine. The laboratory method is after all the only safe one.

In Vienna you found men taking the most indigestible mixtures. Surgeons were "brushing up" in neurology. Gynecologists were taking a little dab from the Freudian School. Many men were listening to the

> Standards and conditions of practice have completely changed in almost every instance. Where 30 years ago we spoke of cure, we now speak of prevention.

refinements of the differential diagnosis to the specialties who know almost nothing of the fundamentals. Most of the patrons of this great medical lunch counter get wildly enthusiastic, but they understand little of what they are eating and you are reasonably certain that they will have mental indigestion of the worst kind if they do not actually become seasick on the return and lost it all. What few misgivings they may have are obliterated by the general air of enthusiasm and the thought that nobody at home is any the wiser.

Physicians at large are now beginning to appreciate the laboratory method in medical education and do not cling to didactic teaching of this lunch counter variety. It is a much easier thing to eat a meal set before you than to prepare the meal for your own delicatation. But you cannot learn cooking from eating, neither can you learn medicine from hearing it taught. A reason for the discontinued popularity of European study is because the general public is educated to the fact that that kind of work and study does not mean knowledge, and a diploma in a foreign language does not now carry conviction with it.

Among the blessings which this country will receive from the Great War is the development of post-graduate teaching in this country. Already every big school in the United States has established this department and most of them recognize the need and are doing their work conscientiously and well. Post-graduate work can no longer be looked upon as a summer lark, it is work and hard work. Medicine is progressing so rapidly that busy practitioners cannot keep up with the times unless they give up practice. Medical journals are all very well but what general practitioner reads half as much as he should? In order to really add to his knowledge he must give up his practice and go to school again. If he doesn't the public is not going to think as much of him. Few people realize the extent and rapidity with which medical knowledge is being spread through the popular press and the dissatisfaction of people with a physician whom they think is behind the times. Physicians are coming into practice better and better trained. When a man completes one and one-half to two years' training in a large city hospital and starts in practice he has an immense advantage over the general practitioner who has been in practice 15 years. If he has ability, he is immediately received into a community unless it be an overcrowded city. But if he gets busy he soon begins to shirk his work. He cannot keep up to the refinements of diagnosis and practice that he was taught unless he has great ability and can sacrifice some fees to the equipment of a laboratory and hire an assistant. The public as yet are not willing to pay more for this kind of work and yet the physician cannot give it as cheaply as he used to give his services without an equipped and manned laboratory.

What compromise or plan is going to work out we do not know but it certainly is not right for a man to practice worse than he knows how. And yet there is as great a need as ever for the family physician. Human hearts do not change with the development of science. They cry out for sympathy and encouragement as they always did. How may it be supplied? Can the old time general practitioner be restored? Will he ever again hold the confidence and implicit faith of the family as he used to? He will be transformed and restored but it must be through the development of cooperation in medicine. It seems almost inevitable that the near future will develop a new kind of practice based on cooperation both on the part of the public and on the part of the profession. Several such schemes are on foot.

A statistical study of small communities would show that each one of a population ranging between 4,000 and 6,000 souls supports six to eight physicians all fairly busy and generally speaking making a fair living. Such communities pay their physicians perhaps $16,000 a year; the two busiest receiving $3,000 to $4,000 each and the others $2,000 or $3,000. Aside from physicians' fees the patient medicine business would claim easily $8,000. This means approximately $25,000 a year for sickness in a community averaging 5,000 souls. Could this money be better spent through cooperation? There is no doubt of it. Such as scheme as is put in practice at the University of California would give the people incomparably better service. If the community hired five physicians representing surgery, medicine, eye, ear, nose and throat and skin, obstetrics and pediatrics and maintained a laboratory with a man in charge to take care of X-ray work and routine diagnostic methods, they would pay no more. These men must all work together in harmony, meeting daily and maintaining a dispensary and consulting with each other about difficult points; learning to know families better than it was ever possible for the old time physician because of the gain in efficiency by division of labor; creating for the community a situation in medicine almost ideal. In larger communities perhaps two such organizations might be built up to favor healthy competition and keep the standard of practice high. The physician would be on a fixed and adequate salary. Is there any reason why he should not be on a professional salary instead of allowing him to do retail commercial work? Should he not be willing to receive a fixed sum for the use of his time?

This of course is only a skeleton of what might be done. There are many widely discussed plans for cooperative medicine on foot. The public may soon seize their opportunity and begin some such organization. Any group of individuals could do it. Neither the public nor the profession seem progressive enough to move forward with any degree of courage in these matters. But the men with vision assure us that this establishment of cooperation in medicine is only a matter of time.

An Insider's Perspective to Clinical Navigation

Martin Medina, BS

In 2014, I had the privilege of helping launch "Clinical Navigation," a pilot program at Children's Hospital of Wisconsin. At the time, I was based at Next Door Pediatrics, a primary care clinic located in one of Milwaukee's poorest neighborhoods. There, I screened patients for social and environmental determinants of health and then assisted their families in navigating the complex community resource landscape. It was a challenging experience that helped reinforce the importance of holistic care in providing better patient health outcomes and overall patient satisfaction.

Growing up in Milwaukee, I was aware of the health disparities present within the urban population and knew that one day I wanted to help address this injustice. When I heard about the Clinical Navigation pilot, I knew I had to be part of it. I was working to get into the University of Wisconsin (UW)-Madison's physician assistant (PA) program, and while I was confident UW Madison would help me to become a top-notch medical professional, I knew my medical training alone would not be sufficient to address all the factors that affect health. To me, this program represented an essential learning opportunity that would give me a foundation to build upon as a future PA.

Going into the experience, I was really optimistic about what I could accomplish. I was partnering with a great health care organization and I learned that the hospital's Population Health Department had gone to great lengths to model the program after Health Leads, a national evidence-based program that trains students to both identify and intervene on behalf of needs, like housing, food, job training, and childcare.

A large part of my time at Next Door Pediatrics initially involved learning about the resource landscape in Milwaukee and partnering with organizations like IMPACT 211, which specialize in connecting residents of southeastern Wisconsin with social services. I found that Milwaukee is actually very resource rich, with an abundance of organizations and programs that provide assistance to families with a wide array of needs. However, I also discovered that these services were disjointed, spread across multiple agencies, and ranged from local and state government welfare programs to grassroots food assistance initiatives run out of church basements.

It took me months to make sense of it all, which I quickly realized was likely a barrier for many people. If it took me months to connect the dots between community resources, how likely was it that a family could quickly and successfully find appropriate resources in a time of need? I also learned the availability and eligibly requirements for many programs and services changed constantly, perpetuating confusion and the ability for families to access services. This was by far the biggest challenge and source of frustration in my work with patient families, however it reinforced the importance and need for programs like Clinical Navigation.

If it took me months to connect the dots between community resources, how likely was it that a family could quickly and successfully find appropriate resources in a time of need?

Working with families in the program was both delightful and heartbreaking. There was nothing more rewarding than helping a family find a food pantry for an acute food need or helping a mom find affordable childcare. However, many other cases were complicated, stemming from a multitude of chronic, lifelong, systemic issues resulting from poverty.

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These cases were the most challenging and often ended with unsuccessful resolutions.

While Milwaukee is a resource rich community, certain resources like affordable housing are in high demand and sparse. Several cases involved families in homeless or emergent homeless situations that involved hours of phone calls to shelters, the Milwaukee Housing Authority, and various other nonprofits. It was frustrating and nothing felt worse than telling a family I had nothing to give them. However, it was those experiences that gave me a greater appreciation for the patient population I was serving.

From the viewpoint of the patient's families, Clinical Navigation provided a rare opportunity to talk openly about their life struggles and prevent what might have otherwise been a predicament managed alone or in secrecy. A safe, nonjudgmental environment, an empathetic listener, and validation of frustrations was sometimes just as important to families as finding a resolution to their social needs.

Time will tell how programs like Clinical Navigation impact patient health outcomes. Ultimately, their efficacy is based on the availability of resources. Communities need to address gaps in services like affordable housing and behavioral health, in addition to coordinating services and allowing people with the highest needs to access services first. However, despite the lack of some resources, an immediate benefit of programs like Clinical Navigation is increased patient care satisfaction.

I spent 12 months volunteering with the Clinical Navigation program before being accepted into the UW MPH and PA program. I believe anyone going into medicine should spend time working in a program like Clinical Navigation. Providing better patient health outcomes for my future patients will require understanding how to address and advocate on behalf of all the determinants that affect health. I believe my experience with Clinical Navigation and my subsequent training in public health and medicine will give me the tools to better tackle the health challenges facing my community.

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The More Things Change...

John J. Frey III, MD, Medical Editor

This issue of the *WMJ* reprints, in its entirety, an article by H.P. Greeley first published in the *Wisconsin Medical Journal* 100 years ago.[1] It is remarkable. The article serves as a window on history just after the 1911 publication of the Flexner report, which was used by organized medicine early in the 20th Century as a rationale to radically reform medical education and shrink the number and variety of schools in the United States.[2] Doctor Greeley, who received his medical degree before that time, reflects on the rapid changes in medicine in the late 19th and early 20th Centuries. Wisconsin had 3 medical schools in 1911: the University of Wisconsin Medical College with 49 students; the Milwaukee Medical College, loosely related to Marquette University, with 191 students; and the Wisconsin College of Physicians and Surgeons, affiliated with Carroll College, with an enrollment of 60 students. The quality of medical schools nationally was extraordinarily varied. Flexner describes the available clinical facilities in the Wisconsin schools from "ill equipped" to "utterly wretched."[3]

Greeley's article was both a vivid description of the life of the general practitioner in communities and a thoughtful explanation of why, even in the early part of the last century, the "old time practitioner" was being pushed aside. "His practice was his school, in which he was continually learning. Life was his laboratory. The natural result was one of the noblest works of God, a physician whose human kindliness was his most glorious attribute, of whose passing the world may say 'Oh, the difference to me'."

But science and increasingly hospital-based training was influencing education, diseases were changing and, in many cases, new ones were rising. Infectious diseases were already beginning to decrease and surgical treatment of many previously fatal problems was on the rise. The increased visibility of specialists was driven by the experiences of pre- and post-World War I physicians spending anywhere from a few weeks to 2 or 3 months in Europe which, Greeley wrote, gave them a "halo of superiority" by being able to say they had "studied abroad in Vienna." For economic reasons, it was very unlikely that general practitioners (GPs) would "study abroad" anywhere but Milwaukee or Chicago so the prestige associated medical travel "abroad" would not trickle down to a GP in Little Chute or Randolph.

But that changed when, as Greeley wrote, one of the consequences of the Great War was the development of post graduate education in the United States. He also wrote about the need for practicing physicians to "go back to school" to keep up, and he celebrated the increasing quality of education that new physicians had compared to their older colleagues. He also wrote that "human hearts do not change with the development of science. They cry out for sympathy and encouragement as they always did."

One hundred years ago, Greeley's solution lay in his emphasis in cooperation in medicine, with physicians from different backgrounds meeting daily, consulting with each other, supported on a fixed and adequate salary, doing the work of caring for a community together.

One hundred years ago, Greeley's solution lay in his emphasis in cooperation in medicine, with physicians from different backgrounds meeting daily, consulting with each other, supported on a fixed and adequate salary, doing the work of caring for a community together. He hoped the "public" would demand and support this idea of a group of clinicians banded together for the common good, but in the end, expressed doubt whether the public or the profession had the courage to pull it off. We are still waiting.

Beyond the Medical Schools

Greeley's vision of collaborative groups of physicians has always informed the practice of

medicine in Wisconsin. Large groups have been a distinguishing characteristic of organization of medicine in the state almost since his time, and 2 articles in this issue of the *WMJ* demonstrate that these organizations can deliver quality care for even the most complex medical and surgical problems.

Smith and colleagues from the Gundersen Health System describe their experience with the use of an anterior exposure for spinal surgery in the surgical training program at their organization.[4] The rate of intraoperative and postoperative complications in their 15 year experience is comparable to national benchmarks and demonstrates that nonmedical school-based centers can engage in training and clinical care at a high level. A second report from Gundersen discusses the implementation of evidence-based protocols for enhanced postoperative recovery for colorectal surgery.[5] Bray and colleagues show how the adoption of a team approach that involved surgeons, dieticians, anesthesiologists, and nursing resulted in a shorter length of stay, which avoids unnecessary exposure to hospital pathogens, which was associated with increased patient satisfaction and was not associated with adverse effects. Cooperation, as Greeley wrote, really can be a source of better and more satisfying care.

The low uptake of screening for colorectal cancer continues to vex the emphasis on prevention advocated by US preventive guidelines. The reasons are complicated – cultural, cost, and ease of screening have been found to affect different populations.[6] Bray and colleagues[7] outline the state of screening, the new modalities and their benefits, and challenges and evidence-based screening protocols for early detection of colorectal cancers. New screening technologies that are less invasive have the potential to increase the acceptance of screening, particularly in groups that have historically suffered from adverse outcomes related to colon cancers.

A creative approach to the serious problem of getting families and children to eat more wholesome foods is described by researchers from University of Wisconsin – Eau Claire.[8] They used economic incentives in cooperation with local stores in the community and gave coupons for fruits and vegetables to 4th graders from low income families. While the redemption levels were not as high as investigators had hoped, they moved the needle somewhat on what we all know are difficult habits to change. Their study represents a community-wide effort that brought together schools, families, and business.

Finally, drug side effects continue to be one of the most common causes of iatrogenic illnesses and hospital admissions in this country. Two case reports in this issue of the *WMJ* add more examples. One by Rafiullah and colleagues describes a bowel perforation as a result of aggressive treatment for lung cancer with erlotinib.[9] A second from Fan and colleagues[10] demonstrates that contaminants in street drugs, in this case levamisole in cocaine, can cause significant and life-threatening psuedovasculitis. In both cases, stopping the drug helped save the patients' lives. Sometimes, less is better.

Editor's Note: We want to thank Dr. H.P. Greeley's grandson, Hugh and his family, all of whom have deep Wisconsin roots, for sending us their grandfather's article from 1917. From the editor's perspective, it shows how much of what we see as "new" dilemmas of medicine are really not.

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Outcomes of Anterior Exposure for Spinal Surgery at an Independent Academic Medical Center

Travis J. Smith, MD, FACS; Amelia T. Bauer, BS; Kara J. Kallies, MS; Mohammed Al-Hamadani, MBCHB, MPH; Sigurd B. Gundersen III, MD, FACS

ABSTRACT

Introduction: Anterior exposure for spinal surgery has expanded and is used for common spinal procedures, including anterior lumbar interbody fusion, disc replacement, and vertebral corpectomy. With this approach, vascular injuries have been reported ranging from 1% to 25%. The impact of resident participation on intraoperative and postoperative outcomes within an independent academic medical center has not been widely reported. The objective of this study was to determine the incidence of complications during anterior exposure spinal surgery at an independent academic medical center.

Methods: After institutional review board approval, we conducted a retrospective review of medical records of patients who underwent elective anterior exposure for spinal surgery from 2000 through 2014.

Results: The study included 335 patients; 60.3% were female. Thirty-day postoperative complications included surgical site infection (4.2%), urinary tract infection (2.7%), need for blood transfusion (2.1%), retrograde ejaculation (1.2%), and deep vein thrombosis (0.9%). There were 12 vascular injuries overall (3.6%); 2.7% were major vascular injuries. Surgery residents participated in 34% of cases. Resident involvement increased over the course of the study. There was no difference in operative time or complications with resident involvement.

Conclusions: The overall incidence of major vascular injury was 2.7%. Levels of exposure and blood loss were associated with vascular injury. Overall postoperative complication rates as well as major vascular injury rates compared favorably to published benchmarks. Complication rates were unaffected by surgical resident involvement.

INTRODUCTION

Approximately 31 million people in the United States experience low back pain, and 31% to 80% of the world's population experiences a back problem during their lifetime.[1-3] Surgical indications for back pain include degenerative disc disease, radiculopathy, spinal instability, and spondylolisthesis. Recently, anterior exposure of the lumbar spine for orthopedic and neurosurgical procedures have increased in popularity. Benefits to this approach include direct access to the interbody space with improved fusion rates.[4,5] This technique can be used as spinal access for disc replacement, anterior lumbar interbody fusion (ALIF), or a combination.[6] The anterior approach requires dissection and mobilization of peritoneal contents followed by vascular mobilization to provide exposure of the anterior surface of the spinal column. A review of methods and complications of anterior spine exposure identified that comprehensive technical descriptions of these procedures are present in spine surgical textbooks, but not in general or vascular surgical texts.[7] In addition, general surgery resident training for these exposures is not well described. Despite this, general and vascular surgeons frequently are relied upon for these exposures.

Previous studies have documented rates of vascular injuries, wound infection, venous thromboembolism (VTE), lymphedema, and ileus. Most carefully studied have been vascular injuries, ranging from <1% to 25%.[4,5,8-11] These injuries may occur during actual exposure or during the neurosurgical portion of the procedure. Various risk factors for vascular injury have been identified, including obesity, L4-L5 disc space exposure, multilevel exposure, and repeat anterior spine exposure. As medicine grows ever more transparent, patients are interested in knowing institutional, as well as individual surgeon outcomes for procedures. In addition, patients want reassur-

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ance that allowing residents to assist in their care has no additional risk.

The objectives of this study were to examine our experience with anterior spine exposure in an independent academic medical center with a general surgical residency program, specifically to (1) evaluate procedural outcomes, including perioperative complications, (2) delineate the incidence, characteristics, and risk factors of vascular complications, and (3) evaluate the effect of resident participation on perioperative complications and patient outcomes.

METHODS

Our organization is an integrated multispecialty health system with a 325-bed independent academic medical center serving 19 counties in a 3-state region. The accredited general surgery residency program graduates 3 categorical residents per year.

Following Institutional Review Board approval, our electronic medical record system was queried by procedure code to identify all patients who underwent anterior spine exposure from January 2000 through June 2014. Exclusion criteria included pediatric patients (<16 years old) and surgical indications of infection, malignancy, or trauma. We completed a retrospective review of the medical records of patients who met inclusion criteria. Variables included patient demographics and preoperative comorbidities as noted on the preoperative history and physical exam; operative data including operative time, operative room staff, procedure performed, estimated blood loss, and intraoperative complications; and 30-day postoperative morbidity and mortality as documented in the operative notes, discharge summary, and outpatient follow-up notes. The occurrence of hernias was reviewed for the entire duration of follow-up data available for each patient. Surgical site infections were noted if they met Centers for Disease Control and Prevention criteria[12] and if the patient received treatment. Vascular injuries were classified as major or minor based on operative records. Major injuries were defined as injuries to the aorta, inferior vena cava, common iliac vessels, internal or external iliac vessels. Injury to any vessel resulting in ≥250 cc of blood loss also was considered a major vascular injury. Minor injuries were defined as injuries to the lumbar vessels, nutrient vertebral body vessels, or median sacral vessels resulting in <250 cc blood loss.

All patients undergoing elective surgery were evaluated by a neurosurgeon, followed by an exposing surgical team consisting of a general or vascular surgeon and surgical resident to determine surgical candidacy. Preoperative antibiotics consisted of weight-based first generation cephalosporins administered within 1 hour prior to the skin incision. Initially, a patient body mass index (BMI) <30 kg/m^2 was required for surgical candidates; as surgeon comfort and experience increased, a BMI ≥30 kg/m^2 was no longer considered a contraindication. Previous extensive retroperitoneal surgery (excluding previous anterior spinal exposure) or retroperitoneal external beam radiation were considered contraindications to this approach. Significant vascular calcifications in the distal aorta, or common iliacs, defined as ≥50% circumferential calcifications on preoperative imaging, also was a contraindication.

Operative Technique

A 2-team approach was utilized in all cases. General or vascular surgeons provided the desired exposure and wound closure; spine procedures were performed by neurosurgeons. The patient was placed in lithotomy position. Fluoroscopy confirmed vertebral level and incision planning. For single-level approaches, a transverse incision was used. For multilevel exposure, a paramedian incision was used. For exposures of L4-L5 level and above, exposure was obtained from the left side. A preoperative vascular exam was performed and intraoperative pulse oximetry monitored perfusion of the left lower extremity. The anterior rectus sheath was opened transversely and the muscle mobilized laterally. The retroperitoneal space was entered and peritoneal contents were mobilized medially. Iliolumbar vessels were divided 1 level above and below the desire disc space(s). The iliac vessels were then mobilized off the anterior surface of the spine. A fixed retractor system was placed and care transitioned to the neurosurgical team. Closure was performed by allowing the vasculature and peritoneal contents to return to normal anatomic position. The rectus muscle was then approximated to the midline to prevent diastasis. The anterior fascia followed by skin was closed with absorbable suture. At case completion, patients were transferred to the postanesthesia care unit and then to the neurosurgery unit with frequent neurological and vascular exams of the lower extremities at the following intervals: admission, 1 hour, every 2 hours for a total of 4 hours, every 4 hours for a total of 8 hours, then every 8 hours thereafter. Symptom-based evaluations and neurovascular exams also were performed.

During our early experience, exposure of the L5-S1 disc space was obtained in a similar fashion from the left side. Once the peritoneum was mobilized, the L5-S1 disc space was exposed between the iliac vessels requiring double ligation of the median sacral vessels. Beginning in 2011, access for L5-S1 was transitioned to the right side to preserve the left side for subsequent anterior approaches if required.

For multilevel exposures, the inferior most disc space was exposed first. Following completion of the neurosurgical portion of the inferior level, the fixed retractor was replaced to expose the upper level. In all cases, the general or vascular surgeon was available immediately during the neurosurgical portion.

During exposure and closure, categorical surgical residents at all postgraduate years (PGY) participated when available and, when unavailable, a second general or vascular surgeon was present. In preparation for these cases, surgical residents participated in annual cadaver simulation laboratories focused on retroperitoneal and abdominal wall exposures. In general, junior residents

(PGY 1-3) were required to observe 5 cases prior to acting as a surgical assistant. Once they had acted as a first assistant for 5 cases, they acted as primary surgeon with the attending surgeon assisting them with the procedure. Senior residents (PGY 4-5) typically had performed 5 observations and 5 first assistant roles prior to acting as primary surgeon. In all cases, a general or vascular surgeon was scrubbed in with the resident. This provided direct supervision of the residents through all steps of the case. No additional trainees (neurosurgery, orthopedic surgery, or vascular residents/fellows) were present at our institution to participate in these cases.

Statistical analysis included chi-square and Wilcoxon rank sum tests using SAS version 9.3 (Cary, NC). A *P* value <0.05 was considered significant.

RESULTS

Preoperative Characteristics

During the study period, 415 patients underwent anterior spine exposure; 335 patients met inclusion criteria. Previous surgeries included posterior spine surgery, lower abdominal surgery, and anterior exposure spine surgery (Table 1).

Table 1. Preoperative Characteristics

Demographics	N (%)
Sex	
Male	133 (39.7)
Female	202 (60.3)
Age (years) mean ± SD	45.3 ± 12.2
Body mass index (kg/m2)	
< 30	228 (68.1)
30.0-34.9	83 (24.8)
35.0-39.9	22 (6.6)
≥ 40.0	2 (0.6)
Tobacco	
Current	94 (28.1)
Former	105 (31.3)
Never	136 (40.6)
Comorbidities, n (%)	
Hypertension	64 (19.1)
Type 2 diabetes mellitus	17 (5.1)
Chronic kidney disease	3 (0.9)
Peripheral vascular disease	3 (0.9)
Coronary artery disease	3 (0.9)
History of DVT/PE	3 (0.9)
Significant vascular calcifications	4 (1.2)
Past surgical history	
Anterior spine surgery	3 (0.9)
Posterior spine surgery	131 (39.1)
Lower abdominal surgery	97 (28.9)

Abbreviations: DVT, deep vein thrombosis, PE, pulmonary embolism.

Operative Data

Sixty-six percent of cases had 2 attending general or vascular surgeons providing exposure and closure; 34% had a resident present with an attending general or vascular surgeon. Median operative time was 210.0 minutes (Table 2), and was similar among cases with versus without resident involvement (Table 3). Of participating residents, 9% were PGY 1, 27% were PGY 2, 20% were PGY 3, 21% were PGY 4, and 23% were PGY 5. Most patients (80%) underwent single-level procedures. Two hundred thirty-three (70%) patients underwent ALIF, 74 (22%) arthroplasty, and 28 (8%) a combination of the two or another procedure. In 7 patients (2.1%), safe exposure was unable to be obtained and the procedure was abandoned. Reasons for failed anterior approach included failure to obtain retroperitoneal access (n=2) and failure to expose disc space due to patient anatomy (n=5). Fifty-two (15%) patients had a concomitant posterior surgery. These operations included completion of posterior instrumentation (n=47) and posterior fusion (n=5). Almost half of patients had surgery at the L5-S1 disc space (Table 2).

Table 2. Operative Data and Lumbar Disc Space Exposed

Variable	Value
American Society of Anesthesiologists class, n (%)	
I	68 (20.3)
II	225 (67.2)
III	42 (12.5)
Operative time, minutes; median (range)[a]	210 (52–686)
Estimated blood loss, cc; median (range)[b]	100 (0–1800)
Resident present, n (%)	114 (34.0)
Single-level exposure	269 (80.3)
Multilevel exposure	66 (19.7)
Levels exposed, n (%)	
L2-L3	3 (0.9)
L3-L4	12 (3.6)
L4-L5	94 (28.1)
L5-L6	2 (0.6)
L5-S1	158 (47.2)
L4-L5 and L5-S1	56 (16.7)
All other multilevel	10 (3.0)

[a]Operative times were missing for 2 patients.
[b]Estimated blood loss was missing for 68 patients.

Postoperative Outcomes

Intraoperative and 30-day postoperative mortality was nil. The most frequent complication was surgical site infection (Figure). Three patients experienced both an early (<30 day) complication, and a late incisional hernia over the follow-up period. There were no postoperative pulmonary emboli, abscesses, or ureteral injuries. When comparing cases with resident participation to those performed by attending surgeons only, there was no significant increase in complication rates for vascular injury, surgical site infection, urinary tract infection, nerve injury, retrograde ejaculation, deep vein thrombosis (DVT), or ileus (Table 3). Resident participation did not significantly increase mean operative times, length of stay, or overall complication rates (8% vs 14%, *P*=0.793) compared to cases involving attending surgeons only (Table 3). When divided into quartiles by date of surgery, only 25% of cases had resident participation in the first quartile, increasing to 34%

Table 3. Patient Outcomes Based on Resident Involvement in Spinal Surgery

Variable	Resident Present N = 115	No Resident N = 220	*P* value
Mean operative time, minutes	227 ± 82	220 ± 86	0.349
Mean length of stay, days	2.9 ± 2.7	2.9 ± 2.2	0.917
Complication, n (%)			
Vascular injury	5 (4.3)	7 (3.2)	0.554
Surgical site infection	5 (4.3)	14 (6.4)	0.449
Urinary tract infection	3 (2.6)	6 (2.7)	0.999
Nerve injury	0	2 (0.91)	0.548
Deep vein thrombosis/pulmonary embolism	0	3 (1.4)	0.554
Retrograde ejaculation	3 (2.6)	1 (0.5)	0.119

Table 4. Patient Characteristics and Associations With Vascular Injuries

Variable	No Vascular Injury N = 323	Vascular Injury N = 12	*P* value
Body mass index, kg/m^2; mean ± SD	27.5 ± 4.5	28.4 ± 4.6	0.649
Age, years; mean ± SD	44.3 ± 12.2	44.5 ± 11.2	0.635
Vascular calcification, n (%)	4 (1.2)	0	0.999
Past surgical history, n (%)			
Posterior spine surgery	123 (38.1)	7 (58.3)	0.227
Anterior spine surgery	2 (0.6)	0	0.999
Abdominal surgery	91 (28.2)	5 (41.7)	0.336
Retroperitoneal surgery	1 (0.3)	0	0.999
Number of attending surgeons, n (%)			0.226
1	106 (32.8)	6 (50.0)	
2	217 (67.2)	6 (50.0)	
Resident present, n (%)	110 (34.1)	5 (41.7)	0.554
Operative time, minutes; median (range)	209.0 (52.0-686.0)	219.5 (90.0-368.0)	0.876
Length of stay, days; median (range)	2.5 (1.0-29.0)	3.0 (1.5-14.0)	0.184
Estimated blood loss, cc; median (range)	100.0 (0-1500)	250.0 (75-1800)	0.002
Number of levels exposed, n (%)			0.022
1	263 (81.4)	6 (50.0)	
2	56 (17.4)	6 (50.0)	
3	4 (1.2)	0	
Specific level exposed, n (%)			0.049
L5-S1	156 (48.3)	2 (16.7)	
L4-L5	90 (27.9)	4 (33.3)	
L4-L5 and L5-S1	51 (15.8)	5 (41.7)	
Other	26 (8.1)	1 (8.3)	

in both the second and third quartiles, to 52% of cases with resident involvement in the last quartile. No difference was noted in complication rates over time despite changes in surgical approach.

Overall, the mean length of stay was 3.0±2.4 days. Seven patients underwent additional anterior or posterior surgery during their hospital stay; four were planned. Indications for additional surgeries performed via a posterior approach included foraminotomy (n=1), open debridement of wound (n=1), posterior fusion (n=2), and vertebroplasty (n=1). Indications for a second anterior procedure were increased stabilization (n=1) and fascial dehiscence (n=1).

Mean follow-up duration was 5.0±3.6 years. Readmission within 30 days of discharge occurred in 18 patients (5.4%). Reason for readmissions included other planned interventions (n=4), pain control (n=4), hematoma/seroma (n=3), surgical site infection/dehiscence (n=3), lower leg swelling (n=2; one with a documented DVT and the other without evidence of DVT), and other (n=2).

Vascular Injuries

There were 12 vascular injuries, for an overall rate of 3.6%. Of these, 9 were major (2.7%) and 3 (0.9%) were minor. The majority of vascular injuries were to the left common iliac vein (n=7; 58.3%). The remaining injuries were at the junction of venous branches with iliac veins, as well as a single minor injury to a lumbar artery. The majority of injuries were treated with clips to control bleeding (n=8; 66.7%). Only 2 injuries required suture repair, and 2 minor injuries were controlled with pressure and packed with thrombin. Among the 12 patients with a vascular injury, failure of case completion occurred in one patient due to failure to expose disc space due to patient habitus/vasculature. One patient with a vascular injury required admission on postoperative day 21 due to a symptomatic VTE involving the left iliac vein and subsequently underwent percutaneous thrombolysis/thrombectomy.

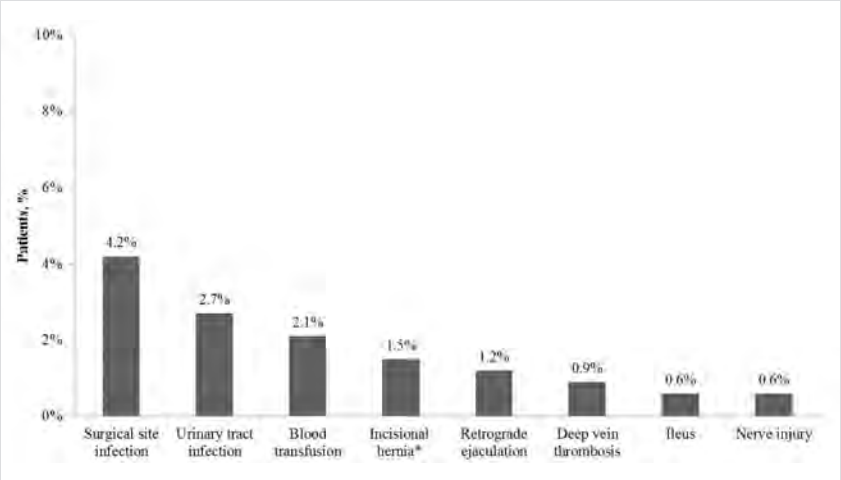
When comparing patients with a vascular injury versus those without, there were no associations between BMI, age, previous surgery, or vascular calcification (Table 4). Estimated blood loss was greater in patients with vascular injury. Number of attending surgeons, resident involvement, operative time, and length of stay were not associated with vascular injury (Table 4). Patients with 2-level exposures were more likely to have a vascular injury than those with only 1 level of exposure. No patient with a 3-level exposure sustained an injury. Exposure of L4-L5 alone or combination with other levels resulted in an injury rate higher than all other exposures (Table 4).

DISCUSSION

Anterior exposure for spinal surgery, which included general surgery resident participation, was associated with a high immediate

success rate (97.9%) and low complication rates at our community teaching hospital. These outcomes compare favorably to benchmarks. Although resident participation has been studied in various neurosurgical procedures, our study is unique in that it focused solely on anterior exposures and the distinct set of complications that can occur with this approach within an independent academic community medical center. The unique aspects within our organization and this study include (1) immediate availability and presence of faculty and resident surgeons for the duration of the case, as opposed to only being present during exposure and closure; (2) resident participation included only categorical PGY 1-5 general surgery residents, as no neurosurgery, orthopedic surgery residency programs exist at our teaching institution. These exposures provide excellent opportunities for teaching without significantly increasing operative time or complication rates. Given that nationally the majority of anterior spine exposures are provided by general or vascular surgeons, this is an important component of training.

Figure. Postoperative Complications



Incisional hernias included any occurence throughout the follow-up period. All other complications were limited to 30 days postoperative.

As surgical training and surgical needs in the United States evolve, general surgeons are increasingly seeking fellowship training, and minimally invasive surgical techniques including laparoscopy and robotic surgery are increasingly common. Similarly, many vascular surgical procedures previously performed in an open fashion are transitioning to endovascular techniques. Anterior spine exposures provide residents with open surgical experience, including open vascular experience with arterial and venous dissection, vascular mobilization, and injury management. The multiple benefits of open vascular surgical experience have been supported in vascular surgical/fellowship training.[13] These skills also translate well to the management of trauma patients. Urban or metropolitan general surgeons as well as fellowship-trained general surgeons can benefit from experience with anterior spine exposure.

The results of our study were similar to those reported in a systematic review of the literature.[5] Wood and associates reported a vascular injury rate of <5% in anterior lumbosacral surgery. Adverse effects of vascular injury were infrequent, but included thrombosis, pulmonary embolism, and prolonged hospital stay. Others have identified more significant morbidity following vascular injuries, with some requiring reoperation to control bleeding, fasciotomies for compartment syndrome, or revascularizing an extremity with stent placement or bypass surgery.[5,9-11] In our series, the vascular injury rate was 3.6%. Major vascular injuries occurred in 2.7% and resulted in little morbidity and no additional surgeries. While patients who experienced a vascular injury had a slightly longer length of stay, the difference was not significant.

Multilevel exposures at L4–L5 and L5-S1 have been associated with increased rates of vascular injury, often due to the need for mobilization of the left common iliac vessels.[5,8-11,13] Consequently, the left common iliac vein is a common site of injury.[4,11,14] Our experience was similar as we observed a greater rate of vascular injury among patients with combined L4-L5 and L5-S1 exposure, and those with exposure of L4-L5 alone. The left common iliac vein injury was most frequently injured (58.3%). BMI was not associated with vascular injury; the maximum BMI was 43.7kg/m^2.

Overall, postoperative complications included low rates of surgical site infection, urinary tract infection, blood transfusion, retrograde ejaculation, and DVT. The most frequent complication encountered was surgical site infection in 4.2% of cases. This was similar to the literature, in which SSI rates up to 4.8% have been reported.[11] The rates of urinary tract infection and blood transfusion in our series were 2.7% and 2.1% respectively, which are slightly higher than other reports of anterior spine exposure, with urinary tract infections reported in 0.6% of patients and blood transfusions in 1.5% to 1.9%.[8,10] Retrograde ejaculation has been reported in 0.9% to 6.3% of cases[15-17] and occurred in 1.2% of our patients. VTE has been reported from 0% to 2.0%[18] and occurred in 0.9% of our patients. In a review of the literature, Ikard reported a 0.7% mortality rate after anterior exposure of the thoracic and lumber spine.[7] Perioperative mortality was nil in our series.

Recent studies have suggested that increased complication rates occur with resident involvement in emergency general surgery procedures and in spinal arthrodesis procedures.[19,20] Schoenfeld and colleagues analyzed data from the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) concerning patients who underwent spinal arthrodesis from 2005 to 2010.[20] Residents were involved in 33% of cases. Using a multivariate model, they found that resident involvement was associated with increased risk of surgical site infection (OR 1.04 [1.02-1.06, 95% CI]; $P<0.001$) and thromboembolic disease (OR 1.9 [1.2-3.1, 95% CI]; $P=0.006$). In contrast, Bydon et al and Lim et al also independently analyzed NSQIP data for neurosurgical cases from 2006 to 2012 and 2011, respectively.[21,22] The proportion of resident participation observed in those studies was 49% and 52% of cases, respectively. Both Bydon et al and Lim et al found a higher overall complication rate among cases with resident participation (18.8% vs 11.2%, $P<0.001$; and 20.12% vs 11.7%, $P<0.001$, respectively). However, after controlling for potential confounding factors (case volume, age, sex, BMI, tobacco use, wound class, American Society of Anesthesiologists class, medical comorbidities, steroid use, operative time, surgical history), resident participation was not an independent risk factor for increased complications.[21,22] Lim et al found residents were more likely to be involved in more complex neurosurgery cases with longer operative times.[22] Although they observed higher rates of surgical site infection and VTE in cases with resident participation, these differences were not significant in a multivariate analysis.

Our series identified no difference in the frequency of vascular injury, surgical site infection, urinary tract infection, blood transfusion, retrograde ejaculation, VTE, ileus, or nerve injury with trainee involvement. By excluding cases of infection, malignancy, or trauma from our series, we were able to compare a homogenous neurosurgical patient population. The immediate availability of attending surgeons during the neurosurgical portion of the procedure and the elective nature of these procedures may contribute to the positive perioperative outcomes.

As institutional experience and surgeon comfort with these procedures increased, restrictions decreased—specifically surgery was offered to patients with BMI>30kg/m^2 and those who had previous lower abdominal surgeries. In addition to this change, operative approach to L5-S1 also was modified, but resulted in no difference in complications. Finally, resident involvement increased over time, which also resulted in no significant changes in outcomes.

At our independent academic medical center, we have a longstanding history of training general surgeons who choose to practice in rural settings. Our graduates have a broad scope of practice, including many general surgical, urologic, and gynecologic procedures.[23,24] Anterior spine exposure requires dissection and mobilization of the abdominal wall, which is applicable to complex ventral hernia repairs including retrorectus approaches and component separation. The vascular exposure and mobilization requires a command of the retroperitoneal and pelvic anatomy and vessel manipulation. Ureter identification and preservation during this procedure increases residents' comfort with colorectal and gynecologic procedures that require ureter identification. These cases provide valuable opportunities to enhance resident's operative experience, which are applicable to many additional general and vascular surgical procedures.

Limitations of this study include the inherent limitations of a retrospective, single institution study. Minor vascular injuries may be underreported if these were felt to be of no consequence during the procedure and not documented by the surgeon. Although the small number of vascular injuries observed in this study was encouraging, the small sample size made it difficult to detect any potential predictors of vascular injury. Another limitation is that no universal criteria exist to define a vascular injury in this setting. Exposures were evaluated over a 14-year period. Over this period, there may have been a learning curve, and the approach for L5-S1 exposure has evolved. In addition, improvements in anesthesia and neurosurgical care pathways occurred. These changing variables also may have contributed to the inability to identify specific patient variables as risk factors for complications. The inability to completely characterize resident involvement with a retrospective study design is also a weakness. Despite these limitations, we believe that this series is representative of outcomes in a community teaching hospital within an integrated health system.

Anterior spine exposures provided safe, reliable access for neurosurgical procedures. The overall incidence of major vascular injury for elective anterior spine procedures at our institution was 2.7%. Levels of exposure and greater intraoperative blood loss were associated with frequency of vascular injury. We were unable to identify preoperative characteristics associated with an increased risk of vascular injury. Postoperative complication rates and major vascular injury rates compared favorably to benchmarks in the literature. These low complications rates were unaffected by surgical resident involvement.

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Implementation of an Enhanced Recovery After Surgery Program for Colorectal Surgery at a Community Teaching Hospital

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ABSTRACT

Introduction: Perioperative programs aimed at decreasing surgical stress to colorectal patients can reduce hospital length of stay and morbidity while improving the patient's perception of the surgical experience. Our goal was to transform patient care from a perioperative platform based on individual physician and nurse choice to a standardized evidence-based Enhanced Recovery After Surgery (ERAS) protocol for all patients undergoing elective colorectal resections.

Methods: An institutional review board-approved retrospective review was performed for the first 12 months of ERAS protocol-driven patient care in 2014 and compared to the prior 12 months (2013) of individual choice managed care.

Results: Ninety-nine patients and 92 patients underwent elective colorectal surgery in the post-ERAS and pre-ERAS period, respectively. The post-ERAS group experienced a shorter length of stay (4.9±2.7 vs 6.2±4.0 days, P=0.001), were more likely to advance to a general diet on postoperative day 1 (72% vs 9%, P<0.001), and had quicker return of bowel function (2.3±1.8 vs 2.8±1.1 days, P<0.0001) compared to the pre-ERAS group. Thirty-day complications were similar between the post-ERAS and pre-ERAS groups and included anastomotic leak (4% vs 0%, P=0.120), surgical site infections (4% vs 8%, P=0.990), and abscess (3% vs 3%, P=0.990). Eleven (11%) post-ERAS patients and 7 (8%) pre-ERAS patients were readmitted within 30 days postoperative (P=0.410).

Conclusion: We implemented change through a new system of care based upon standardized evidence-based ERAS protocols through the preoperative, intraoperative, and postoperative patient experience. In the first year of the ERAS program, patients experienced a reduced length of stay without a significant difference in morbidity or mortality.

INTRODUCTION

Enhanced recovery after surgery (ERAS) protocols have been developed to improve patient care in recent years. The primary goal of these protocols is to reduce patients' surgical stress response, decrease postoperative morbidity and mortality, decrease the length of hospital stay, and improve patients' perception of the surgical experience.[1-3] The development of ERAS protocols involve multimodal changes during the preoperative, intraoperative, and postoperative periods to focus on patient preoperative preparation, nutrition, fluid management, early mobilization, advancement of diet, and prevention of complications.

In patients undergoing elective colorectal surgery, implementation of the ERAS protocols have resulted in shorter hospital stays without significantly impacting morbidity and mortality.[3-7] Patient satisfaction scores with these protocols using validated measures have suggested increased satisfaction with postoperative pain and fatigue.[8] Economic evaluations of colorectal ERAS protocols have indicated a beneficial effect, supporting their cost-effectiveness.[7]

Our goal was to implement a standardized ERAS pathway for all patients undergoing elective colorectal resections at our community teaching hospital based on previously published protocols, and compare patient outcomes before versus after ERAS implementation.[2] This would change our institution's practice pattern from a perioperative platform based on individual physician and nurse choice to a standardized evidence-based ERAS protocol. We hypothesized that, despite our previously demonstrated shorter lengths of stay[9-11] compared to other reports in the literature,[3] a further decrease in length of stay and 30-day complication rates would be observed after implementation of an ERAS protocol for patients undergoing elective colorectal resection.

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Table 1. Practice Changes Introduced with ERAS Protocol Implementation

Preoperative	Intraoperative	Postoperative
Preadmission patient education	Intraoperative fluid management	Minimize narcotic pain management
Preoperative isovolemic bowel preparation	Active prevention of hypothermia	Early mobilization
Decreased preoperative fasting with preoperative carbohydrate loading	Prevention, treatment of postoperative nausea, vomiting	Early initiation of diet Prevention of ileus-Alvimopan
Single dose oral/IV antimicrobial prophylaxis	Laparoscopic assisted surgery Transverse incision	Early urinary catheter removal
Prevention of ileus-Alvimopan	Removal of nasogastric tubes	Chemical and mechanical VTE prophylaxis
	No peritoneal drain placement	Postoperative IV fluid restriction

Abbreviations: ERAS, enhanced recovery after surgery; IV, intravenous; VTE, venous thromboembolism.

METHODS

The implementation of a standard preoperative, intraoperative, and postoperative ERAS protocol at our medical center occurred in January 2014 after several key steps. We followed a "Plan, Do, Study, Act" model to facilitate a smooth transition from an era of patient care based on provider preference to one with a standardized protocol used by all clinicians. First, the appropriate settings, roles, and resources needed to succeed were identified. A core group of surgeons and surgical residents reviewed the available literature on ERAS, including an evidence-based care pathway from the 2009 ERAS Group Recommendations from Lassen et al.[2] In addition, members of a core planning committee attended a conference with presentations focused on colorectal ERAS programs.

Our institution is an integrated multispecialty health system serving 19 counties over a 3-state region. The medical center at the main campus includes a 325-bed teaching hospital. At the time of ERAS introduction, there were 18 attending surgeons, 15 general surgery residents, and 1 minimally invasive/bariatric surgery fellow within the surgery department. The entire general surgery staff and resident surgeons were educated on the ERAS approach and reported the benefits and principles of an ERAS protocol. Once the core team established a framework of ERAS principles to guide patient care preoperatively, intraoperatively, and postoperatively, it was presented within the general surgery department. A review period was allowed to address concerns with the protocol. To gain support from the Anesthesia Department, meetings also were held with the department chair. With a base from the ERAS Society, a final protocol was developed that included some areas of compromise in order to gain buy-in from the general surgery and anesthesia departments.

After support was obtained from attending surgeons and resident providers, principles were presented and education provided to general surgery clinic nurses, preoperative and postoperative nurses, anesthesia care providers, pharmacists, nutritionists, electronic medical record personnel, and patient education services. The specific aspects of care pertinent to the different care providers were discussed. A "nurse champion" was established on the preoperative and postoperative surgical unit to help with clarifying ERAS protocols. In addition "surgical champions" – the surgeon authors – were designated for all hospital staff to approach with questions or concerns.

Updated patient education material describing the anticipated steps of ERAS was developed and given to patients at their preoperative appointment and reviewed again by postoperative nurses each day of the patient's hospitalization. Order sets were created and standardized in the electronic medical record system.

The protocol was implemented first in a pilot program with modifications and additional teaching completed as necessary, and we ensured buy-in of the protocol from all groups prior to full roll-out. At 3 months post implementation, areas of noncompliance were identified and addressed with the noncompliant individuals and at a system level, and changes were made. The goal of these interventions was to create a smooth transition to a standardized protocol for use in the perioperative care of elective colorectal surgery patients.

The agreed upon ERAS protocol included the initiatives presented in Table 1. All areas of change focused on reducing surgical stress and included updated patient education, decreased preoperative fasting with preoperative carbohydrate loading, intraoperative fluid restriction, active prevention of hypothermia, alvimopan administration preoperatively and postoperatively, minimization of narcotic pain medication, and early initiation of diet. Anesthesia providers were instructed to use a goal-directed administration of intravenous (IV) crystalloid based on vital signs and urine output. Alvimopan, a mu-opioid receptor antagonist, was administered in a single preoperative dose and postoperatively twice daily until return of bowel function. Alvimopan was not used with patients who were on chronic narcotics. An attempt to minimize narcotics postoperatively was made by using acetaminophen and nonsteroidal anti-inflammatory drugs, including toradol, as adjuncts.

In order to evaluate the outcomes of the ERAS protocol, Institutional Review Board approval was obtained, and a retrospective review of the medical records of all patients who underwent elective colorectal resection with or without ostomy creation (total colectomy, sigmoidectomy, transverse colon resection, right or left hemicolectomy, or cecetomy) after protocol implementation

Table 2. Preoperative Characteristics and Perioperative Outcomes

Variable	Pre-ERAS	Post-ERAS	*P* value
N	92	99	
Sex, n (%)			0.980
Female	50 (54)	54 (55)	
Male	42 (46)	45 (45)	
Mean Age, years	65.4 ± 12.6	63.1 ± 14.4	0.240
ASA Class, n (%)			0.047
I	6 (7)	7 (7)	
II	37 (40)	57 (58)	
III	48 (52)	33 (33)	
IV	1 (1)	2 (2)	
Laparoscopic approach, n (%)	59 (60)	65 (71)	0.110
Mean operative time, (minutes)	208 ± 76	206 ± 77	0.64
Pathology, n (%)			0.67
Benign	62 (67)	64 (65)	
Malignant	30 (33)	35 (35)	
Mean number of PODs	6.5 ± 4.0	5.2 ± 2.7	<0.001

Abbreviations: ERAS, enhanced recovery after surgery; ASA, American Society of Anesthesiologists; POD, postoperative day; NG, nasogastric.

(January 2014 – December 2014) was completed. Patients in the post implementation (post-ERAS) group were compared to patients who underwent elective colorectal surgery during the year prior to ERAS implementation (January 2013 – December 2013; pre-ERAS group). Pediatric patients (<18 years of age) were excluded from the study. Statistical analysis included Wilcoxon Rank Sum and Fisher's Exact tests. A *P*-value < 0.05 was considered significant.

RESULTS

Overall, 191 patients met inclusion criteria for this study. Ninety-two patients were included in the pre-ERAS period of individual provider preference and 99 in the post-implementation group. The patient groups were similar in age and sex but the post-implementation group had a lower American Society of Anesthesiologists (ASA) class compared to the pre-ERAS group (Table 2). There was no difference between groups for the rate of laparoscopic approach, the mean operative time, or the pathology of the colon (Table 2).

The mean intraoperative fluid volume administered was 2562 cc pre-implemenation compared to 2124 cc post-implementation (*P*=0.009). In the post-ERAS group, Alvimopan was used preoperatively in 83% of patients and postoperatively in 84%, compared to only 12% and 14%, respectively, in the pre-ERAS group (*P*<0.001). In both groups, most patients received some narcotic pain medication for postoperative pain control. The post-ERAS group had reduced use of patient-controlled analgesia (PCA), which resulted in significantly less IV opioid consumption (Figure 1). This led to an overall decrease in IV narcotic use and increase in oral narcotic usage. The median oral morphine equivalents increased from 22.5 to 45.0 in the pre-ERAS vs post-ERAS groups (*P*=0.038). Patients in whom an open approach was planned were offered an epidural; this did not change post-implementation (Figure 1).

Eighty-one percent of patients were given a liquid diet on the night of surgery, and 72% were advanced to a general diet on postoperative day 1 (Figure 2). Bowel function returned earlier in the post-ERAS group, at a mean of 2.3 ± 1.8 postoperative days vs 2.8 ± 1.1 days pre-implementation (*P*<0.001). There was no significant difference in the number of nasogastric tubes placed after surgery between the groups (16% pre-ERAS vs 8% post-ERAS; *P*=0.080). Based on early initiation of diet, use of mu-opioid antagonists, and use of nonnarcotic pain medications, the adherence to the protocol was 75%.

Post-implementation patients had a shorter postoperative length of stay than the pre-ERAS group (Table 2). There were no statistically significant differences in 30-day complications (Figure 3). The 30-day readmission rate was 8% and 11% pre-implementation and post-implementation, respectively (*P*=0.46). The reasons for readmissions in the pre-ERAS group included abscess (n=2), urinary tract infection (n=2), urinary tract infection and ileus (n=1), urinary tract infection and surgical site infection (n=1), and hematoma (n=1). In the post-ERAS group, reasons included anastomotic leak (n=4), intraabdominal abscess (n=3), perianastomotic air without a leak (n=1), failure to thrive (n=1), nausea/vomiting (n=1), and exacerbation of congestive heart failure (n=1).

DISCUSSION

Our community teaching hospital's general surgery department developed a protocol-based care pathway for our elective colorectal surgery patients that affected all aspects of perioperative care. Through a multimodal, team-based approach, we were able to gain cooperation from all groups involved and create a culture change by transitioning from an individual provider preference pathway to a standardized, evidence-based ERAS pathway. Challenges to ERAS implementation included gaining support from anesthesia, surgical, and nursing staff. These challenges were addressed by reviewing the existing evidence for each ERAS measure while making some modifications to the protocol based on input from each group. After initial protocol implementation, feedback from participating departments was considered and addressed. While a decrease in intraoperative fluid per case was observed, we did not designate an anesthesiology champion for ERAS measures; future adopters of ERAS protocols should consider this when implementing such a protocol. Nursing time constraints to provide preoperative and postoperative education was a concern among nurses under pressure to do more work in the same patient encounter. These constraints were recognized and collaboration with nursing leadership allowed for the appropriate

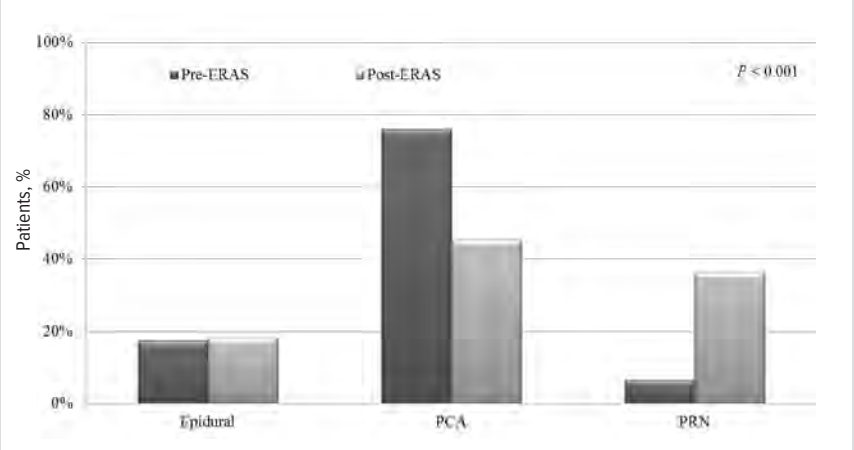
support. Adherence to the ERAS protocol was approximately 75%.

Overall, integration of the protocol produced favorable results. No changes to surgical techniques were implemented; as such, surgical approach, operative times, and pathology were similar pre- and post-implementation. The protocol resulted in reduced intraoperative fluid administration, reduced PCA usage, earlier advancement of diet and return of bowel function, and a shorter hospital length of stay (LOS).

The early advancement of diet and quicker return of bowel function observed in the post-ERAS group may have contributed to the shorter LOS, which, in turn, may have been associated with a quicker return to normal daily activities and decreased resource utilization—an important consideration in the current era of cost-containment in health care. Aarts et al performed a multivariate logistic regression analysis of ERAS principles which indicated that preoperative counseling, intraoperative fluid restriction, laparoscopic approach, postoperative initiation of clear fluids, and early removal of the urinary catheter were independently associated with a shortened LOS.[12]

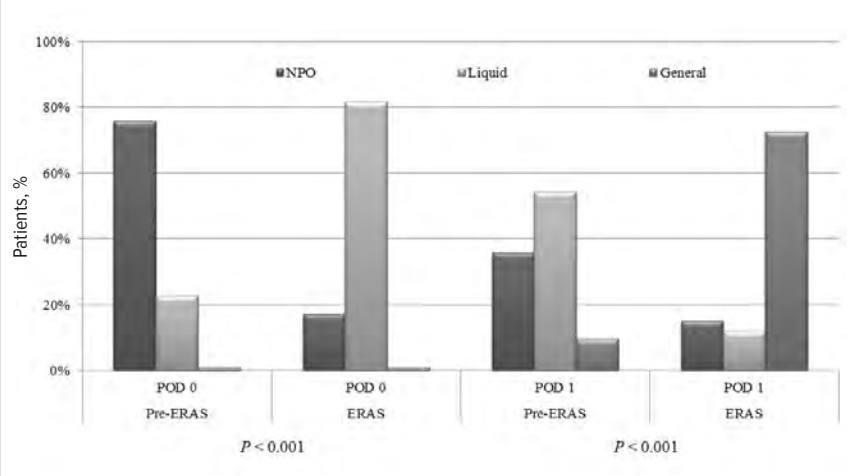
Thirty-day morbidity and mortality was similar pre- and post-implementation. While the pre-ERAS group is notable for an anastomotic leak rate of zero, we believe that this represents an exceptionally favorable year. Historically, our anastomotic leak rate has ranged from 0.4% to 3.2%.[9-11] The post-ERAS anastomotic leak rate is consistent with our institution's outcomes over the past decade.

Figure 1. Modalities Used for Postoperative Pain Control



Abbreviations: PCA, patient-controlled analesia; PRN, as needed; ERAS, enhanced recovery after surgery.

Figure 2. Postoperative Advancement of Diet



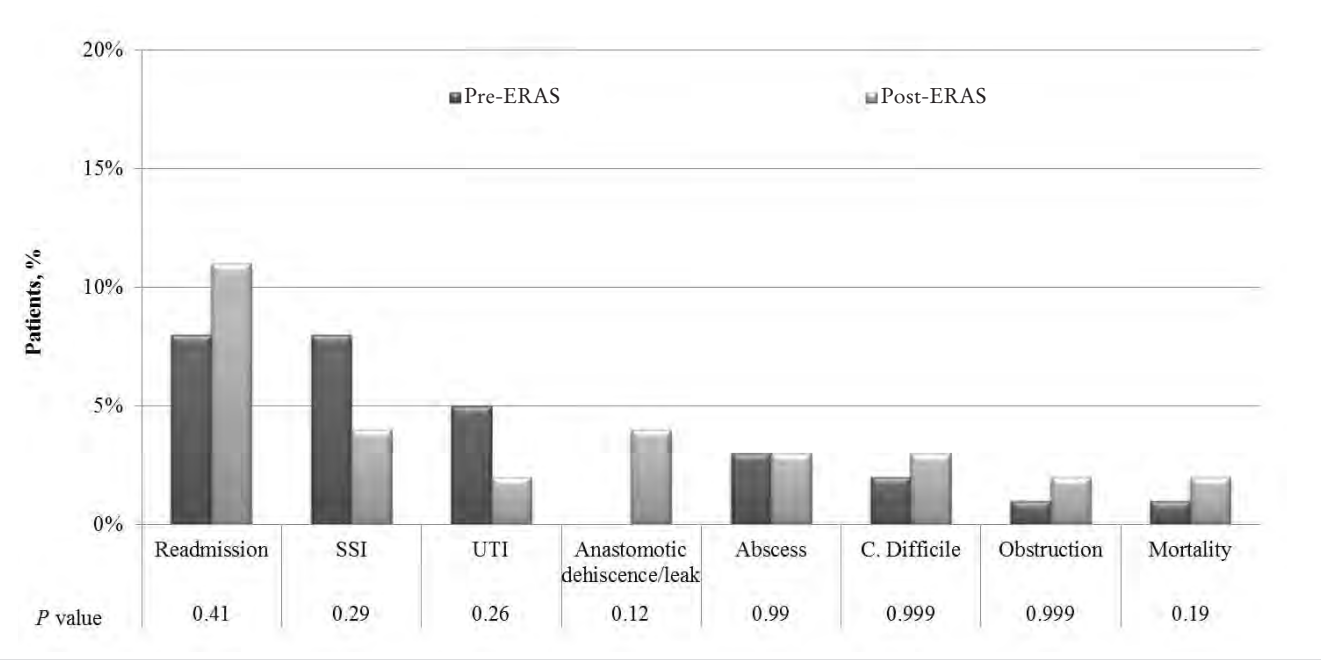
Abbreviations: NPO, nothing by mouth; POD, postoperative day; ERAS, enhanced recovery after surgery.

The 30-day readmission rate was slightly higher in the post-ERAS group, which may be attributable to the anastomotic leaks. In the pre-ERAS group, 4 of the 7 readmissions were for urinary tract infections (UTI). The ERAS protocol included early removal of urinary catheters, which may have prevented UTI-related readmissions. Although the difference in readmission rates pre- and post-intervertion was not statistically significant, it warrants further investigation.

The outcomes of ERAS in this study were comparable to those reported in a comprehensive meta-analysis of ERAS data in the literature;[3] however, our outcomes were improved with respect to minor complication rates including urinary tract infections, surgical site infections (6.1% vs 39.4%), major complication rates including sepsis, anastomotic leak, reoperation, ileus, abscess, and *C. Difficile* infection (14.3% vs 21.2%), and 30-day mortality rates (2.0% vs 1.3%), respectively. The length of stay in our series was 5.2 days, which was comparable to those reported in the literature, ranging from 4 to 7.4 days.

Limitations to this study include its retrospective nature, limited sample size, and single institution experience. Most of the core ERAS group recommendations were adopted; however, the practice of mechanical and antibiotic bowel preparation was continued as part of an ongoing quality improvement effort to reduce the rate of surgical site infection within our medical center. Adherence to each protocol component was encouraged, but not required, and there were no strict discharge criteria during the study period. Additionally, patient satisfaction and return to activ-

Figure 3. Thirty-Day Postoperative Readmission, Morbidity and Mortality



Abbreviations: SSI, surgical site infection; UTI, urinary tract infection.

ity were not evaluated. Future research on these protocols should include patients' satisfaction with their surgical experience and perceived pain control.

This study illustrates the feasibility of ERAS implementation at a community-based, integrated multispecialty health system. It also highlights the importance of multidisciplinary care and a collaborative, evidence-based approach to practice change. Despite the fact that no changes in surgical techniques occurred, patient care was positively affected by the protocol. In bringing the change full circle, we have distributed these data within our health system to provide feedback and reinforce the benefits of the change.

CONCLUSION

An ERAS protocol for elective colorectal surgery was successfully implemented at our community teaching hospital. Implementation of the protocol led to a culture change within our medical center, and improved patient care by decreasing the length of stay, without an increase in surgical morbidity and mortality. This study highlights the importance of a multidisciplinary collaborative approach to change preoperative and postoperative patient care in order to improve patient outcomes.

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Colorectal Cancer Screening

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ABSTRACT

Colorectal cancer (CRC) continues to be one of the most commonly diagnosed cancers and contributes significantly to many cancer-related deaths despite sustained progress in diagnostic and treatment options. Many forms of CRC can be prevented through early and routine screening, when precancerous lesions may be detected and removed before they undergo malignant transformation or metastasis. Despite widespread efforts to improve CRC screening rates, at least 40% of age-eligible adults do not adhere to screening guidelines. A new generation of noninvasive, molecular-based diagnostic tests with high sensitivities and specificities has the potential to improve screening rates through optimal risk stratification of patients who may benefit from more invasive screening techniques. This review presents various guidelines and methods that are currently available for CRC screening, summarizes the rationale behind utilization of novel molecular-based diagnostic tests for CRC screening and prevention, and discusses appropriate screening techniques and intervals in populations of varying risk.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second most common type of cancer-related death in the United States. In 2013, 136,119 people were diagnosed and 51,813 people died from CRC in the United States.[1] The cumulative lifetime risk for colon cancer is 1 in 20 in men and 1 in 22 in women.[2] Death rates from colon cancer have been on the decline in the United States, which is primarily attributable to the adoption of widespread screening that allows for early detection and removal of colorectal polyps. Moreover, substantial improvements in colon cancer treatment have been achieved over the past few decades.[3] However, CRC rates are increasing in historically low-risk countries such as Japan, Korea, and China and in eastern Europe.[4] Higher colon cancer rates reported in these geographic areas likely result from westernization of global diets, obesity, smoking, alcohol consumption, lack of exercise, instability in the microbiome, and carcinogenic substances in food.[5-10]

The purpose of this review is to present current guidelines and methods available for CRC screening, discuss novel molecular-based CRC diagnostic tests, and discuss appropriate screening techniques and intervals in various populations. In order to gather information for this review, we searched recent CRC screening guidelines, related articles, and appropriate references using the PubMed database.

COLORECTAL SCREENING GUIDELINES

Colonoscopy and other screening modalities have contributed to decreased rates of colon cancer death through early identification and removal of precancerous polyps.[11] With the advent of novel molecular technologies and increased understanding of the molecular changes leading to cancer, new methods hold promise for risk stratification of patients to determine those who may benefit from more invasive screening tests.[12] Importantly, recent guidelines released by the US Preventive Services Task Force (USPSTF) in June 2016 confirmed that CRC screening in average-risk, asymptomatic adults between the ages of 50 and

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CME available. See page 33 for more information.

Table 1. Comparison of Various Screening Recommendations Issued by Different Organizations for Average-Risk, Asymptomatic Individuals

Organization	Year	Age to Begin Screening (Years)	Age to Discontinue Screening (Years)	Tests Recommended for Cancer Prevention and Interval/Procedural-Based Tests	Tests Recommended for Cancer Detection and Interval/ Stool-Based Tests	Preferred Screening Method	Ref
US Preventive Services Task Force	2016	50	75	Colonoscopy (10 yrs) Flexible sigmoidoscopy (5 yrs) Flexible sigmoidoscopy with FIT (sigmoidoscopy every 10 yrs, FIT every 1 yr) CT colonography (5 yrs)	FOBT (1 yr) FIT (1 yr) FIT with stool DNA (1 or 3 yrs)	None	13
American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, and American College of Radiology	2008	50	Not specified	Colonoscopy (10 yrs) Flexible sigmoidoscopy (5 yrs) CT colonography (5 yrs) Double-contrast barium enema (5 yrs)	FOBT (1 year) FIT (1 year) Stool DNA (interval uncertain)	Cancer prevention	14
American College of Physicians	2012	50	75 or individuals with <10-year life expectancy	Colonoscopy (10 yrs) Flexible sigmoidoscopy (5 yrs) Stool DNA (interval uncertain)	FOBT (1 yr) FIT (1 yr)	None	15
American College of Gastroenterology	2009	50 (45 for African Americans)	Not specified	Colonoscopy (10 yrs) Flexible sigmoidoscopy (5 yrs) CT colonography (5 yrs)	FIT (1 yr) FOBT (1 yr) Stool DNA (3 yrs)	Cancer prevention (colonoscopy) over detection (FIT)	16

Abbreviations: Ref, reference; FOBT, fecal occult blood test; FIT, fecal immunochemical test; CT, computed tomography.

75 years is substantially underused despite its demonstrated benefits.[13] Moreover, these guidelines suggest that although the multiple screening strategies described later in this article have differing levels of evidence to support their utility, there are no data that shows that a select test provides a greater net benefit. In addition to these USPSTF guidelines, other organizations including a joint venture between the American Cancer Society (ACS), the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology,[14] the American College of Physicians (ACP),[15] and the American College of Gastroenterology (ACG)[16] also have issued CRC screening guidelines for cancer prevention and detection strategies. While all organizations recommend routine CRC screening beginning at age 50 in asymptomatic average-risk adults, preferred screening methods, frequency intervals, and age to discontinue screening vary across guidelines. Similarities and differences between these guidelines are summarized in Table 1. As discussed later in this article, guidelines from the various organizations also differ with regard to the definition of high-risk individuals and optimal screening strategies in these patients.

COLORECTAL SCREENING OPTIONS

As described below and in Table 2, numerous procedural- and laboratory-based screening modalities with variable sensitivity, specificity, positive/negative predictive values, and cost have emerged to expand the list of available CRC screening methods. Due to high sensitivity and specificity and facilitation of immediate polyp removal, colonoscopy remains the gold standard for CRC screening. Thus, it follows that a major limitation of imaging-, stool-, and blood-based testing modalities is the potential for a two-step approach where individuals with a positive screening test are advised to undergo follow-up colonoscopy. This may result in early diagnostic gaps and the potential for diagnostic delays or patients lost to follow-up. Moreover, given the low sensitivity of stool- and blood-based tests for precancerous polyps as compared to colonoscopy, a larger number of precancerous polyps have the potential to go undetected and untreated. As the impact of two-step CRC methods on patient compliance with follow-up testing is unknown, shared decision making with physicians should occur prior to screening. In particular, patients should be informed of the risks and benefits of screening and how a positive test result will be managed prior to screening. On a similar note, patient recollection of dates and results from prior colonoscopies is unreliable and consultation of medical records is therefore important for verification of screening history and interval.[17]

Procedural-Based Screening

Colonoscopy has been widely available since the 1970s, at which time it was used for polypectomies. Screening guidelines became widely adopted in the 1990s based on randomized controlled trials demonstrating that CRC screening with fecal occult blood testing (FOBT) followed by a colonoscopy for a positive result

Table 2. Comparison of Sensitivity and Specificity of Various Screening Modalities for Detection of Colorectal Cancer[30,47]

Test	Sample	Sensitivity	Specificity	Positive Predictive Value[a]	Negative Predictive Value[a]	Availability	Approximate Cost Before Insurance
Colonoscopy	Anatomic	95%	90%	0.4%	>99.99%	Specialist	$800 - $1,000*
FOBT	Stool	70% (64%-80%)	92.5% (87%-96%)[18]	0.4%	>99.98%	In-vitro diagnostic	$5[b]
FIT	Stool	70% (61%-91%)	95% (91%-98%)	0.6%	>99.98%	In-vitro diagnostic	$22[b]
CT colonography	Imaging	89% (84%-93%)	75% (59%-87%)	0.1%	>99.99%	Radiology	$400 - $800[b]
ColonSentry	Blood	72%	70%	0.1%	>99.98%	Laboratory developed test	Up to $350[c]
SEPT9-based tests	Blood	67%-96%	81%-99%	0.1%-3.9%	>99.98%->99.99%	Laboratory developed test	Up to $350[c]
Cologuard	Stool	92% (83-98%)	87% (86-87%)	0.3%	>99.99%	Laboratory developed test	$649[d]

Abbreviations: FOBT, fecal occult blood test; FIT, fecal immunochemical test; CT, computed tomography.

[a]Calculated based on prevalence rate of 41.9 CRC cases/100,000 (age adjusted to the 2000 US standard population) obtained from the American Cancer Society/North American Association of Central Cancer Registries 2015 (https://cancerstatisticscenter.cancer.org).

[b]Obtained from Colon Cancer Alliance: http://www.ccalliance.org.

[c]Based on general estimates for blood-based DNA amplification tests.

[d]Obtained from Cologuard website: http://www.cologuardtest.com.

was associated with a significant reduction in colon-cancer related mortality.[19,20] Observational studies demonstrated a 30% to 60% reduction in the risk of incident CRC and mortality from isolated screening colonoscopy versus colonoscopy based on positive FOBT results.[21,22] Colonoscopy remains the current standard of care in the United States for CRC screening, and the USPSTF recommends colorectal screening for individuals between the ages of 50 and 75.[13,23] Currently, the most common screening algorithm used in the United States for average-risk individuals involves a colonoscopy every 10 years based on the slow growth cycle (10-15 years) for most small polyps to grow and transform into CRCs.[11] Decreased interval screening is indicated when there is a family history of CRC or when high-risk polyps have been identified.[24,25] Despite high-quality published societal guidelines, screening in the United States is limited to approximately 58% of at-risk men and women.[26]

Flexible sigmoidoscopy also is included for colorectal screening in the United States guidelines as reductions in CRC incidence and mortality have been demonstrated with this procedure.[27] When used for screening, flexible sigmoidoscopy is recommended every 5 years in average-risk individuals. As the benefits of sigmoidoscopy are limited to the distal colon, this approach has been utilized largely for screening in cases where a full colonoscopy may not be initially feasible. Such technical limitations may be due to obstructive cancer, extensive looping of the colon, traverse angulation, or excessive mucosa friability. Given the gradual shift from left-sided CRC to right-sided CRC that has been consistently observed since the 1960s, colonoscopy continues to dominate endoscopic screening modalities.[28,29]

In recent years, use of computed tomography (CT) colonography has replaced the double-contrast barium enema as the radiographic screening alternative to colonoscopy.[16] However, CT colonography remains controversial and this procedure is generally not covered by insurance unless there are contraindications to other more traditional forms of CRC screening.[30] When used for screening, the suggested interval is 5 years in average-risk individuals, but this recommended interval is somewhat uncertain until additional data become available.[31] Like colonoscopy, CT colonography requires bowel cleansing and colon distention for an optimal study. The procedure itself is relatively fast, well-tolerated, and does not require anesthesia or a post-procedural recovery period. The radiation dose is approximately 4-5 mSv (for reference, a 2-view chest x-ray is about 0.1 mSv), which may be further reduced using optimized protocols to decrease radiation exposure.[32] Unfortunately, CT colonography does not allow for simultaneous polyp removal or determination of the histologic nature of a lesion and false positive/negative CT colonography findings may result from residual material and/or insufficient distension. It is also important to note that extracolonic findings, the majority of which are benign and not clinically significant, have the potential to add unnecessary health care costs and anxiety, although clinically significant lesions may be detected at earlier, more treatable stages as well.[32] Studies have shown mixed

Table 3. Varying Definitions of Increased-/High-Risk Individuals According to Screening Guidelines

Organization	Description of Increased/High-Risk Individuals	Additional Notes	Reference
US Preventive Services Task Force	Family history of CRC (a first-degree relative with early-onset CRC or multiple first-degree relatives with CRC)	Older age, male sex, and African-American race at higher risk for development of CRC	13
American Cancer Society, US Multi-Society Task Force on Colorectal Cancer, and American College of Radiology	Family history of CRC, polyps, or hereditary CRC syndrome; personal history of CRC, chronic inflammatory bowel disease (ulcerative colitis or Crohn's disease)		14
American College of Physicians	Risk factors include age, African-American race, family history of CRC, polyps, or hereditary CRC syndrome (especially before age 50 years)	Individualized risk assessment should be performed by clinicians to determine when to begin screening	15
American College of Gastroenterology	Patients with a single first-degree relative diagnosed with CRC or advanced adenoma before age 60 years or those with 2 first-degree relatives with CRC or advanced adenomas	Patients with a single first-degree relative diagnosed with CRC or advanced adenoma at age 60 years or older are considered average-risk	16

Abbreviation: CRC, colorectal cancer.

sensitivity and specificity for small lesions <5 mm as compared to larger lesions >9 mm.[30] In general, the accuracy of polyp detection by CT colonography improves with increasing lesion size and is comparable with traditional colonoscopy for polyps 10 mm or larger.[31] However, the detection of flat polyps and those smaller than 10 mm by CT colonography is inferior and should be considered when weighing screening options.[31]

Laboratory-Based Screening

Annual or biennial fecal occult blood testing (FOBT) and fecal immunochemical testing (FIT) are widely available and frequently used for CRC screening. These tests identify at-risk individuals based on the presence of microscopic blood in the stool and are considered very cost-effective relative to colonoscopy (Table 2). Colorectal polyps tend to be more friable and thus bleed more readily compared to normal colonic mucosa, making detection by this test a viable screening method. FOBT and FIT are based on different analytical principals as FOBT indirectly detects blood through nonspecific, peroxide-mediated oxidation of guaiac that may be affected by diet and/or chemicals.[33] In contrast, FIT utilizes an antiglobin antibody that is specific for detection of human hemoglobin.[33] Therefore, it follows that screening with FIT has superior sensitivity and specificity compared to FOBT due to the use of human-specific globin antibodies that are not affected by diet or medications.[34] Moreover, although consecutive testing of multiple FOBT samples increases the sensitivity of the test, only 1 sample is required for FIT screening.

Effectiveness of fecal screening has been demonstrated in randomized controlled trials (RCT),[22] and in populations where colonoscopy is underutilized, alternative testing results in fewer CRC deaths.[35] Regardless, fecal-based screening tests have been criticized for their low sensitivity despite relatively high specificity (Table 2) and this has resulted in practitioner concerns over legal liability for missed lesions.[36] As a result, adoption of FOBT or FIT for primary population screening has been limited in the United States. Several nations around the world—including Australia, Canada, France, and Spain—with insufficient colonoscopy capacity or low acceptance of the colonoscopic approach, utilize these assays and several rely on these tests exclusively for screening.[22,25] It is important to note that lack of availability or acceptance (as opposed to cost savings) tends to drive fecal screening programs. Recent evidence suggests that colonoscopy as compared to an initial FIT approach is a more cost-effective method for screening adenoma, advanced neoplasia, and a composite endpoint of advanced neoplasia or stage I CRC.[37]

Genetic-Based Screening

Both genetic and epigenetic alterations contribute to CRC. As described below, targets of the new molecular CRC screening methods include abnormal proteins or mRNA expression, gene mutations, or aberrantly methylated genes present in stool or body fluids. These tests are based on fundamental findings such as the identification of microsatellite instability and hypermethylated CpG (cytosine-phosphate-guanine) islands in gene-promoter regions that facilitate tumorigenesis of various cancers including CRC.[38,39] Hypermethylation of CpG islands in gene promoters can silence tumor suppressors. Similarly, hypomethylation of repetitive genetic elements can turn on oncogenes or create other genomic instability. Additional epigenetic alterations that have been identified in CRC involve the *APC, CTNNB1, KRAS*,[40] *BRAF, SMAD4, TGFBR2, TP53, PIK3CA, ARID1A, SOX9, FAM123B*, and *ERBB2* genes.[12]

New molecular-based modalities based on genetic and epigenetic alterations have emerged and are changing the approach to CRC screening. In October 2014, the Centers for Medicare and Medicaid Services announced that it would provide reimburse-

Table 4. Genetic Syndromes That Increase Risk for Colorectal Cancer[49]

Syndrome	Responsible Genetic Mutation	Description	Recommended Age of Screening Onset (Years)	Recommended Screening Method and Interval	Additional Notes
Familial adenomatous polyposis (FAP) gene	Tumor suppressor *APC*	Development of numerous polyps by teenage years; eventually exhibit hundreds to thousands of colorectal polyps; average age of onset of CRC is 39 years; risk of CRC approaches 100% by age 45	10-12	Colonoscopy or flexible sigmoidoscopy (1 year)	Patients with a milder variant [attenuated FAP (AFAP)] characterized by development of <100 polyps require slightly less aggressive screening that can begin at a later age and be repeated every 1-2 years
Lynch syndrome or hereditary nonpolyposis colorectal cancer	Mismatch repair genes *LH1, MSH2*, *MMSH6*, or *PMS2*) or a related gene, *EPCAM*	Most common form of inherited CRC; tumors exhibit microsatellite instability involving changes in the length if nucleotide sequence repeats in tumor DNA; lifetime risk of CRC is 80%	20-25 or 10 years younger than the earliest case in the family	Colonoscopy (1-2 years)	Families with *MSH6* or *PMS2* mutations require less aggressive screening at the risk of CRC is less diagnosis later
MUTYH-associated polyposis (MAP)	Base excision repair gene *MUTYH*	Most commonly found in patients presenting with 20 to 99 adenomas; lifetime risk of CRC in biallelic carriers is 70%-75%	25-30 years	Colonoscopy (1-2 years)	
Juvenile polyposis syndrome	Tumor suppressor genes *SMAD4* or *DMPR1A*	Development of dozens to many hundred juvenile polyps in stomach, intestine, colon, and rectum; generally diagnosed in the first 2 decades of life; risk of CRC approaches 68% by age 68	12	Colonoscopy (1-3 years)	
Peutz-Jeghers syndrome	Cell polarity gene *STK11*	Defined by distinct hamartomatous polyps and characteristic mucosal and cutaneous pigmentation; lifetime risk of CRC is 39%	8	Colonoscopy (variable based on initial findings)	Additional increased risk for gastrointestinal and extra-intestinal cancers
Hereditary mixed polyposis syndrome	Unknown	Originally described in large Ashkenazi Jewish family; affected individuals exhibit several different types of polyps and adenocarcinomas; mean age of polyp occurrence is 28 years	20	Colonoscopy (1-2 years)	
Serrated polyposis	Unknown	Predisposition to serrated polyps and development of CRC; estimated lifetime risk of CRC is >50%	20	Colonoscopy (1-2 years)	

ment for the first FDA-approved, noninvasive stool-based DNA test from Exact Sciences (Cologuard) for average-risk patients. This test evaluates the presence of blood (immunochemical assay for human hemoglobin) and DNA (aberrantly methylated *BMP3* and *NFRG4* promoter regions, *KRA*S mutations, and β-actin expression) in a patient's stool sample that may be indicative of precancerous or cancerous polyps. Cologuard is currently recommended every 3 years in average-risk individuals that fit the screening parameters.[41] Advantages of the test include the avoidance of bowel preparation, performance of the test at home without any time lost from work, and absence of any procedural-related complications. The cost of Cologuard, while higher than that of FIT or FOBT, remains less than colonoscopy (Table 2). Moreover, this multitarget testing has been shown to have higher sensitivity than FIT[42,43] that is on par with standard colonoscopy for CRC detection. As the number of private insurance companies accepting this alternative continues to expand, this novel modality is likely to be integrated into a new algorithm for cost-effective screening.

Several blood-based molecular tests are also available in the United States, including Quest Diagnostics' ColoVantage, Abbott's mS9, Epi's proColon, and GeneNews' ColonSentry. ColoVantage, mS9, and proColon all are based on the *SEPT9* gene. The product of the *SEPT9* gene gives rise to a septin protein involved in cytokinesis and exhibits aberrant methylation of its promoter region in CRC tissue as compared to normal colonic mucosal tissue.[44] Although the original *SEPT9*-based tests have lower sensitivity as compared to Cologuard, next-generation *SEPT9* tests such as proColon 2.0 have optimized polymerase chain reaction (PCR) protocols with improved sensitivity. Of note, in April 2016 Epi's proColon was the first blood-based test to be approved for CRC screening by the FDA.[13] In contrast, ColonSentry is based on a

7-gene messenger RNA panel (including the A*NXA3, CLEC4D, LMNB1, PRRG4, TNFAIP6, VNN1*, and *IL2RB* genes) that is thought to reflect subtle alterations in peripheral gene expression in response to disease as opposed to serving as direct, tumor-derived biomarkers.[45,46] Sensitivity of the ColonSentry test is similar to that observed for the first-generation *SEPT9* tests. As shown in Table 2, sensitivities of these blood-based tests are lower than that of Cologuard or colonoscopy.[47]

Screening Methods for Increased-Risk and High-Risk Patients

Among the many accepted cancer screening methods and intervals, the majority are considered appropriate for patients at average-risk. Approximately 70% of CRC is considered sporadic or average-risk and has an average age of onset of 69 years old. While the lifetime risk of colon cancer is reported at approximately 5%, individuals with 1 first-degree affected relative have a 2- to 3-fold increased risk and individuals with 2 first-degree affected relatives have a 3- to 4-fold increased risk.[48] Definitions of increased-/high-risk based on personal history, family history, and/or genetics differ slightly across guidelines and are summarized in Table 3. ACG guidelines recommend that increased-risk and high-risk patients utilize colonoscopy as their screening method as negative results from alternative approaches are not sufficient to negate the need for colonoscopy due to the high pretest probability of disease. In general, ACG guidelines also suggest that screening should occur every 5 years starting at age 40 or 10 years younger than the earliest diagnosis in the family.[16] Additional detailed protocols that involve screening more often and at an earlier age for individuals at increased-/high-risk for CRC have been reported in CRC screening guidelines as well.[14,16]

The remainder of CRC occurs in high-risk individuals with genetic CRC syndromes or inflammatory bowel disease.[11] Specific conditions that convey an increased genetic risk include FAP (along with Gardner syndrome and Turcot syndrome), Lynch syndrome or hereditary nonpolyposis colorectal cancer, juvenile polyposis syndrome, Peutz-Jeghers syndrome, and mutY Homolog (MUTYH)-associated polyposis.[14,48-50] As summarized in Table 4, patients affected with these syndromes require further adjustments to screening schedules, including earlier and more frequent examinations. With increased genetic testing, additional familial mutations will likely be identified in the near future.

SUMMARY

Colonoscopy and other screening modalities have contributed to decreased rates of colon cancer death through early identification and removal of precancerous polyps. Together with updated USPSTF screening guidelines, the emergence of a variety of more sophisticated and noninvasive tests with greater sensitivities and specificities is beginning to shift the paradigm of CRC screening. In countries where there are limited financial and personnel resources or in situations where patients opt for an initially less invasive test, a two-step approach is a reasonable consideration and remains aligned with current screening practices. However, prior to choosing a two-step screening method, patients must be informed of the benefits and limitations of current screening options and understand that a positive test result would lead to further invasive diagnostic testing through colonoscopy. Following the appropriate lag time for implementation, new screening strategies have the potential to lead to further reductions in health care costs by providing a targeted and individualized approach to colonoscopic examination.

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Duodenal Perforation Secondary to Erlotinib Therapy in a Patient With Non-Small Cell Lung Cancer

Rafiullah, MD; Wardah Sayed Shah, MBBS; Navid Abdul Majid, MD; Rezwan Islam, MD

ABSTRACT

Lung cancer is a lethal disease with high mortality, and treatment modality varies with type of tumor and stage of the disease. Targeted molecular therapies have been developed for patients with advanced non-small cell lung cancer. The presence of epidermal growth factor receptor (EGFR) mutation qualifies the patient for EGFR-TKI (tyrosine kinase inhibitor) therapy such as erlotinib, which is not without risk. We report an interesting case of duodenal perforation secondary to erlotinib therapy. This is the second reported case of bowel perforation after erlotinib therapy in a patient with advanced non-small cell lung cancer.

INTRODUCTION

According to most recent statistics, there are 526,510 individuals in the United States living with a history of lung cancer. It is estimated that an additional 224,390 cases will be diagnosed in 2016, with the median age at diagnosis of 70 years,[1] although it has been reported that the number of lung cancer deaths has declined due to a decrease in smoking frequency.[2] The choice of chemotherapy, surgery, radiotherapy, or a combination of therapies depends on the type of lung cancer, staging, and performance status of the patient, as well as patient choices. These therapies all can have substantial side effects and complications.[3]

Research in the field of non-small cell lung cancer (NSCLC) has revealed that it is a combination of a heterogenous group of pathologies. Adjuvant chemotherapy is one of the most important treatment strategies for NSCLC. Research has shown cisplatin-based regimens have demonstrated survival benefits for stage II and stage IIIA disease.[4-10] Targeted molecular therapies have been developed for patients with advanced NSCLC. The presence of epidermal growth factor receptor (EGFR) mutation qualifies the patient for EGFR-TKI (tyrosine kinase inhibitor) therapy such as erlotinib, gefitinib, and afatinib.[11] Testing for EGFR mutation typically occurs only in patients with adenocarcinoma; however, EGFR-TK1 therapy is appropriate for later line treatment of progressive metastatic disease in any histology type. Erlotinib is associated with some serious complications including fatal pulmonary toxicities, liver failure, and hepatorenal syndrome. One rare complication is gastrointestinal perforation. We report a case of duodenal perforation, which is the second reported case of bowel perforation after erlotinib therapy in a patient with advanced NSCLC.[12]

CASE REPORT

A 53-year-old woman with a primary medical history of metastatic squamous cell lung cancer with an anaplastic component of undifferentiated carcinoma with mediastinal lymphadenopathy, who was receiving erlotinib, presented to the oncology clinic with abdominal pain. She had been seen in the oncology clinic 1 day before admission for shortness of breath. She did not have any chest pain and was saturating well on room air. Computed tomography (CT) of the chest showed no evidence of pulmonary embolism. When she presented again to the oncology clinic, she complained of abdominal pain that had started the night before, 8/10 in severity, was right-sided and radiating to the back. She reported nausea but no vomiting, and absolute constipation since morning. She has been compliant with erlotinib therapy for her lung cancer and denied any hematemesis or melena. She was admitted to the

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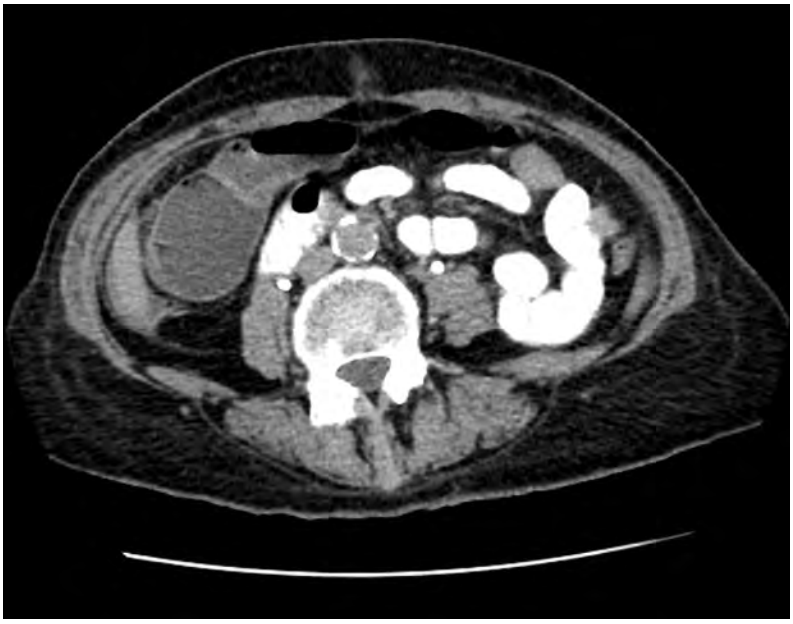
hospitalist service for further workup and management.

The patient's oncology history was significant for metastatic squamous cell lung cancer with anaplastic component of undifferentiated carcinoma diagnosed in July 2012. The cancer was stage IV, (cT3, CN2, cM1), with a right lung mass 6.6 cm x 7.3 cm, with mediastinal lymphadenopathy, 4.8 cm right temporal mass with edema, and right frontal region lesion. Her oncology management included palliative whole brain radiation therapy in August 2012. She received carboplatin AUC 6, paclitaxel (dose 300 mg intravenous [IV] in 500 ml normal saline), and bevacizumab (dose of 1100 mg IV in 100 ml normal saline, added after the third cycle). This regimen was repeated every 3 weeks for 6 cycles, completed in mid-November 2012. Pemetrexed (dose 900 mg IV in 100 ml normal saline) was started in early December 2012 as maintenance therapy. Pemetrexed was stopped mid-March 2013, as her chest CT showed significant progression of disease. Per her oncologist, the patient has squamous cell cancer but also has a component of anaplastic large cells that are undifferentiated. Since squamous cells typically do not respond to pemetrexed, it was stopped. She also received pemetrexed as maintenance therapy every 3 weeks times 5 cycles from December 2012 to February 2013. She was started on erlotinib (dose 150 mg once daily) as subsequent monotherapy in March 2013 for progressive disease based on a chest CT. She had used erlotinib as monotherapy for only 47 days before the current presentation. Erlotinib was stopped in early May 2013 with the hospitalization for acute abdominal pain. After cessation of erlotinib, carboplatin and paclitaxel were started 2 months later in July 2013.

Figure. Computed Tomography of the Abdomen and Pelvis Revealing Evidence of Duodenal Bulb Perforation With Extra Luminal Air Near the Anterior Surface of Liver



On physical examination, the patient was hemodynamically stable with dry mucous membranes. Abdominal examination revealed guarding throughout, with tenderness on the right side of the belly, more prominent in the right flank area and right lower quadrant. She demonstrated guarding and mild rigidity and had hypoactive bowel sounds. CT of the abdomen and pelvis revealed evidence of duodenal bulb perforation with extra luminal air near the anterior surface of liver (Figure). She had a normal appendix, was given nothing by mouth and was hydrated with normal saline. She subsequently underwent laparotomy with repair of the duodenal perforation with omental patch. There was no evidence of bowel metastasis found during laparotomy and on histology of the surgical specimen. The patient had an excellent recovery, and erlotinib was stopped. She was followed by her oncologist and primary care physician with no further complications.

DISCUSSION

Carcinoma of the lung is the 7th leading cancer in women and the 8th leading cancer in men in the United States.[1] Erlotinib is the second-line therapy for refractory and advanced NSCLC. The favorable response factors for erlotinib therapy are female gender, nonsmoker, Asian race, and adenocarcinoma.[13,14] The most frequently reported side effect of erlotinib is skin rash (49%-85%). Other reported complications of erlotinib include diarrhea, anemia, muscle weakness, and, rarely, gastrointestinal perforation. The exact mechanism of erlotinib causing bowel perforation is not clear. Our patient had a history of steroid use (though the duration is not clear) and a vascular endothelial growth factor receptor (VEGFR) inhibitor (bevacizumab), which can potentially cause bowel ischemia leading to peptic ulcer disease. She did not have any record of endoscopy-proven peptic ulcer disease, but she was using proton pump inhibitors for gastrointestinal prophylaxis. There was no documented history of colonoscopy, bowel perforation, bowel surgery, diverticulosis, or any evidence of alternative etiology that may have led to the bowel perforation. Our patient had poor re-epithelization in the presence of erlotinib.

Cheon et al[12] reported the case of a 66-year-old woman who developed an enterocutaneous fistula secondary to erlotinib therapy for metastatic NSCLC. Theirs was the first reported case of

bowel perforation secondary to erlotinib therapy in a patient with NSCLC. Their patient did not have bowel wall metastasis and had received erlotinib for 9 months before the bowel perforation.[12] We are reporting a case of a 53-year-old woman who developed duodenal perforation after erlotinib therapy for advanced metastatic NSCLC. Our case is the 2nd reported case of bowel perforation secondary to erlotinib, similar in many respects to Cheon et al's case: female, similar age group, and NSCLC. Our patient developed duodenal perforation after 47 days of erlotinib, while Cheon et al[12] reported bowel perforation after 9 months of therapy. Our patient also did not have bowel metastasis at time of duodenal perforation.

In June 2012, a CT of the abdomen in our patient did not show any bowel wall metastasis, and the operative specimen of the bowel also did not show any bowel wall metastasis or evidence of cancer. The prescribing information for erlotinib states that patients at a high risk for gastrointestinal perforation and complications are those who have concomitant use of angiogenic therapy (VEGFR inhibitor, eg, bevacizumab), nonsteroidal antinflammatory medications, steroids, and taxane-based chemotherapy. Our patient was receiving only erlotinib as subsequent (not concomitant) monotherapy for 47 days before the duodenal perforation. Patients with a history of diverticular disease or peptic ulcer disease are also at increased risk of gastrointestinal complications secondary to erlotinib.[13,14] Our patient had some of these risk factors, such as previous taxane-based chemotherapy, steroid use, and therapy with bevacizumab. Cheon et al's patient also had some of these risk factors.[12]

CONCLUSION

Gastrointestinal perforation is a rare but potentially lethal complication of erlotinib therapy, especially in patients with risk factors like taxane-based therapy, steroid use, concomitant or previous therapy with bevacizumab, or other gastrointestinal comorbidities such as diverticular disease and peptic ulcer disease. This rare complication of erlotinib should be considered in patients who present with abdominal pain to prevent mortality.

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A Case Report on Suspected Levamisole-Induced Pseudovasculitis

Tiffany Fan; Jeffrey Macaraeg, MD; Toufik Mahfood Haddad, MD; Holly Bacon; Duc Le; Mohsin Mirza, MD; Carrie Valenta, MD; Tammy Wichman, MD

ABSTRACT

Introduction: Levamisole-induced pseudovasculitis should be considered in patients with inconsistent anti-neutrophil cytoplasmic antibodies (ANCA) pattern and history of cocaine use.

Case Presentation: A 50-year-old man presented to the emergency department with symptoms of bilateral pulmonary emboli. His hospital course was complicated by multiple end organ failure, which improved dramatically with prednisone. Although he was diagnosed previously with granulomatosis with polyangiitis due to positive proteinase 3 (PR3), myeloperoxidase (MPO), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) and cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA) markers, his longstanding cocaine use and history of skin ulcers, thrombotic events, and febrile illnesses suggested a diagnosis of levamisole-induced pseudovasculitis instead.

Discussion: Differentiating between vasculitides can be challenging due to similar clinical and laboratory findings. To differentiate the two, biopsies should be obtained. The absence of granulomas or leukocytoclasia, and the presence of vasculopathic purpura, should guide clinicians toward pseudovasculitis.

Conclusion: It is important to maintain a high index of suspicion for pseudovasculitis because long-term corticosteroid use to treat granulomatosis with polyangiitis can lead to detrimental effects.

CASE PRESENTATION

A 50-year-old man presented to the emergency department with increasing shortness of breath, fatigue, and dizziness. On review of symptoms, the patient denied the presence of fever, chills, chest pain, and headache. Vital signs showed a blood pressure of 118/89 mmHg, temperature of 97.5°F, heart rate of 111 beats per minute, respiratory rate of 19 breaths per minute, and saturation of 94% on room air.

Physical examination revealed general illness. Lung examination revealed significant diffuse and bilateral wheezing and +3 bilateral pitting edema was found on both upper and lower extremities. Significant laboratory parameters included a B-type natriuretic peptide of 15,604 pg/mL, a D-dimer of 12.39 mcg/mL, and a white blood cell count of 13.2 x $10^3/mm^3$. Cardiac biomarkers were negative. A computed tomography angiogram was performed, revealing lobar and segmental bilateral acute pulmonary emboli with increased left axillary, hilar, and mediastinal lymphadenopathy. Magnetic resonance imaging also was completed, which showed restricted diffusion throughout both cerebral hemispheres, concerning for a global anoxic event.

Past medical history was significant for hypertension, transient ischemic attack, heartburn, chronic kidney injury, deep vein thrombosis, and pulmonary emboli. During a prior admission, the patient presented with similar respiratory symptoms as well as chronic kidney injury and was suspected of having granulomatosis with polyangiitis due to proteinase 3 (PR3), myeloperoxidase (MPO), perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA), and cytoplasmic anti-neutrophil cytoplasmic antibodies (C-ANCA) serum marker positivity (Table 1). He declined renal biopsy and was treated empirically with prednisone and rituximab. In addition, the patient had a history of provoked deep vein thrombosis in his legs after sustaining bilateral leg trauma and subsequently having difficulty with ambulation. Due to medication noncompliance, he continued to have sub-

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Table 1. History of Biomarker Results

Admission Date	P-ANCA	C-ANCA	MPO	PR3	Cocaine	Levamisole
Feb 2011					+	
Feb 2012	-	+			+	
Nov 2012	+	+	+	+		
Feb 2014				+		
March 2015					+	
May 2015	+		+	+	+	-
July 2015			+	-	+	

Abbreviations: P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3.

therapeutic international normalized ratios, which presumably led to the formation of pulmonary emboli. There was no record of a thrombophilia workup despite these aforementioned provoking factors.

Family history was noncontributory. Relevant social history included heavy use of cocaine.

To treat his bilateral pulmonary emboli, the patient was started on heparin and warfarin therapy. Forty milligrams of prednisone was continued to treat granulomatosis with polyangiitis but rituximab was discontinued. On the fifth day of admission, the patient desaturated and laboratory findings revealed leukocytosis with a white blood cell count of 21.7 x 10^3/mm^3 and a procalcitonin level of 0.12 μg/L, likely due to sepsis. Chest x-ray revealed bibasilar opacities consistent with possible hospital-acquired pneumonia; thus, the patient was started on triple antibiotic therapy with vancomycin, piperacillin/tazobactam, and levofloxacin. Since the patient was immunocompromised, sulfamethoxazole/trimethoprim was subsequently added to cover the possibility of pneumocystis pneumonia. However, he continued to decline and developed severe sepsis with liver, kidney, and respiratory failure. Since no evidence of methicillin-resistant Staphylococcus aureus was found on sputum culture, vancomycin was discontinued. Due to continued rises in procalcitonin and white count, the decision was made to replace piperacillin/tazobactam with meropenem for broader coverage. Clindamycin was added for possible aspiration pneumonia and voriconazole was added for possible fungal infection. Sulfamethoxazole/trimethoprim also was discontinued due to rising creatinine and worsening acute kidney injury and replaced with primaquine. After 2 weeks, all antibiotics except meropenem were discontinued as all cultures remained negative. Due to continued high suspicion for pneumonia, doxycycline was added.

During his hospital admission, a transthoracic echocardiogram was obtained due to clinical deterioration with nonsustained ventricular tachycardia. Results revealed acute systolic heart failure with an ejection fraction of 25% to 30% with global hypokinesis secondary to sepsis. At that time, the possibility of levamisole-induced pseudovasculitis was considered due to the patient's longstanding history of cocaine use. Positive P-ANCA, C-ANCA, MPO, and PR3 serology as well as past medical history of deep vein thrombosis, necrotizing pneumonia, and infectious ulcers also were suggestive of pseudovasculitis induced by a cocaine contaminant known as levamisole. Prednisone was increased to 60 milligrams a day to empirically treat suspected levamisole-induced pseudovasculitis. As the patient's condition began to improve, meropenem and doxycycline were discontinued. Throughout the course of 1 month, the patient slowly recovered from bilateral pulmonary emboli, hospital-acquired pneumonia, acute kidney injury, anion gap metabolic acidosis, hepatic congestion, and acute systolic heart failure. At discharge, his laboratory data and clinical findings were markedly improved compared to baseline.

DISCUSSION

Differentiating between granulomatosis with polyangiitis and its mimics is a challenging but necessary task to prevent the misuse of corticosteroids and immunosuppressant therapy. Use, and particularly overuse, of corticosteroids is associated with immunosuppression, an increased risk of fracture, development or exacerbation of cardiovascular disease, fluid retention, hypertension, and obesity.[1]

Pseudovasculitis is a disease process that mimics the presentation and laboratory findings of true vasculitis (Table 2). It does not, however, present with the typical histopathologic findings usually seen in vasculitis. Cocaine-induced midline destructive lesions should be considered in patients with positive ANCA serology, an atypical set of clinical findings, and a history of cocaine use. Levamisole, a contaminant found in 69% of cocaine,[2] also can cause its own myriad symptoms known as levamisole-induced pseudovasculitis.

Currently, there is no clear consensus for the treatment of cocaineor levamisole-induced pseudovasculitis. Treatments are primarily supportive. Steroids, anticoagulation, and withdrawal from cocaine use have been beneficial in varying degrees.[3] The natural history of levamisole-induced pseudovasculitis is spontaneous resolution without medical therapy. Thus, early recognition and cocaine cessation is the key for treatment.[3]

Overall, our patient presented with bilateral pulmonary emboli and was hospitalized with necrotizing pneumonia. These symptoms, along with a past history of skin ulcers, thrombotic events, and frequent episodes of myalgia, shortness of breath, and febrile illnesses, are suggestive of levamisole-induced pseudovasculitis. In addition, the patient had positive ANCA serology and a longstanding history of cocaine use. Despite these characteristic findings, our patient did not develop necrotic purpura on the helix of his ears or agranulocytosis, two distinctive findings consistent with levamisole-induced pseudovasculitis.

Table 2. Comparison of Granulomatosis With Polyangiitis, Cocaine-Induced Midline Destructive Lesions, and Levamisole-Induced Pseudovasculitis

	VASCULITIS	PSEUDOVASCULITIS	
	Granulomatosis With Polyangiitis[4]	**Cocaine-Induced Midline Destructive Lesions**[5]	**Levamisole-Induced Pseudovasculitis**[6]
Physical Findings	Fever, myalgia, arthralgia	Absent systemic symptoms	Fever, myalgia, arthralgia
Ear, Nose, Throat	Oral/nasal ulcers, sinusitis, rhinorrhea, purulent/bloody nasal discharge	Nasal ulcers, nasal septum perforation, facial ulcers	Purpura on ear helix, zygomatic arch, cheek
Cardiac	Pericarditis, coronary arteritis[7]	Myocarditis	Variable
Pulmonary	Cough, dyspnea, stridor, wheezing, hemoptysis, pleuritic pain	Pulmonary edema, bronchiolitis	Variable
Renal	Variable	Variable	Variable
Cutaneous	Lower extremity purpura, necrosis, ulceration, urticaria	Skin necrosis, urticaria	Skin necrosis, skin ulcers, lower extremity purpura Immunoglobin and complement deposits found in skin[8]
Vascular	Variable	Thrombosis	Thrombosis
Serology	PR3, C-ANCA, P-ANCA, MPO	PR3, P-ANCA, HNE	PR3, C-ANCA, P-ANCA, MPO, HNE, cathepsin G lactoferrin, elastase, lysozyme, agranulocytosis
Histology	Mixed inflammatory infiltrates, leukocytoclastic vasculitis, fibrinoid necrosis, perivenulitis Stromal granuloma with giant cells, micro-abscesses and deeply located necrosis	Mixed inflammatory infiltrates, leukocytoclastic vasculitis, fibrinoid necrosis, perivenulitis	Mixed inflammatory infiltrates, leukocytoclastic vasculitis, fibrinoid necrosis, perivenulitis

Note: This is a partial list and not intended to be all inclusive.

Abbreviations: P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; MPO, myeloperoxidase; PR3, proteinase 3; HNE, hydroxynonenal.

During a prior admission, he tested negative for levamisole after a positive cocaine screen (Table 1). However, testing for levamisole occurred after 48 hours. Ideally, the presence of levamisole should be tested immediately upon admission, as the half-life is 5.6 hours and only 3% to 5% of the drug can be detected in the urine within 48 hours of last use.[6] Since levamisole can only be detected in the urine for up to 48 hours, the negative levamisole result could not be used to rule out the use of levamisole-laced cocaine.[6] Retrospectively, a biopsy of his skin ulcer, testing for hydroxynonenal (HNE) antibodies, and urine toxicology screening for levamisole within 48 hours of admission would have allowed us to confidently make this diagnosis, which unfortunately was not done. On the other hand, a renal biopsy would have been able to confirm granulomatosis with polyangiitis. A high index of suspicion and early diagnosis in a patient with a history of cocaine use is crucial in order to minimize unnecessary treatment that may place the patient at a higher risk for immunosuppression.

CONCLUSION

While differentiating among various vasculitides can be challenging, we must take steps to confirm a patient's diagnosis before initiating treatment, as long-term corticosteroid use can lead to myriad undesirable effects. To differentiate between granulomatosis with polyangiitis and pseudovasculitis induced by cocaine and levamisole, kidney and skin biopsies must be obtained. It is also imperative to check HNE ANCA, Cathepsin G, lactoferrin, elastase, and lysozyme levels and screen for the presence of levamisole in the urine.

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Tracking the Use of Free Produce Coupons Given to Families and the Impact on Children's Consumption

Sydney Chinchanachokchai, PhD; Eric M. Jamelske, PhD; Deborah Owens, PhD

ABSTRACT

Background: American children typically eat fewer fruits and vegetables than recommended by guidelines. This study examines whether free coupons can increase children's fruit and vegetable intake at home.

Methods: Families of the participating students received weekly coupons for fresh fruits and vegetables over a 1-month period. Pretest and posttest surveys were conducted to measure change in consumption. Each survey consisted of 3 consecutive days of self-reported dietary recall of each student's fruit and vegetable intake for dinner.

Results: Coupon redemption across the 4-week study was 27.3%. There was evidence of increased vegetable consumption, but not fruit consumption.

Conclusions: We identified successes and challenges that can guide practitioners, policymakers, and other academic researchers in future endeavors to meet this goal.

INTRODUCTION

Poor nutrition in children contributes to childhood obesity persisting into adulthood and is correlated with increased risks for costly chronic diseases.[1] American children typically eat fewer fruits and vegetables than recommended by the United States Department of Agriculture guidelines.[2] In particular, low fruit and vegetable intake and high obesity rates are significant among low-income households.[3] Thus, the challenge is to find strategies to increase children's fruit and vegetable consumption to promote healthier outcomes, especially for families of lower socioeconomic status.

Many school-based interventions have attempted to increase children's fruit and vegetable intake using a variety of methods during school lunch and snack periods.[4] Results have generally found modest positive effects on children's fruit and vegetable consumption at school. However, many children, especially in low-income families, have limited access to fruits and vegetables at home.[5] Studies also have shown that coupons, vouchers, and price discounts positively impact fruit and vegetable consumption.[6]

The objective of this study was to evaluate an intervention to increase children's fruit and vegetable intake at home by increasing access to these items through free coupons. We addressed 2 primary research questions: (1) At what rate were the free coupons redeemed by families over the study period; (2) Did fruit and vegetable consumption increase for children in families that redeemed most of their free coupons?

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METHODS

Participants

Six classrooms of fourth grade students, three each in 2 Wisconsin elementary schools participated in this study (N=121). Overall, 60% and 75% of students were eligible for free/reduced-price school meals in Schools 1 and 2, respectively. Table 1 presents demographic information for the sample. Parents received a letter notifying them of the study and asking them to return the signed letter only if they did not want their child to participate. Participation was extremely high with only 2 students opting out. Seven area grocery stores also participated by agreeing to accept the coupons.

Materials and Procedure

Coupons—The family of each student received 4 sets of coupons

each containing fifteen $1 coupons valid for 1 week, giving every family $15 each week for a total opportunity of $60 to spend on fresh fruits and vegetables. Figure 1 presents an example of the coupons used in this study.

All coupons were mailed to the families along with instructions on when, how, and where to use the coupons. The coupons were redeemable only for fresh fruits and vegetables because of the added health benefits compared to canned/frozen items. Parents also received information regarding the benefits of eating fresh fruits and vegetables, including recipes to prepare fresh produce.

Procedure—We conducted training meetings with each of the 7 stores to design the coupons and arrange for accepting the coupons at the point of sale. Prior to coupon distribution we administered a pretest survey, followed by 2 posttest surveys given during the second and fourth weeks. Each of these surveys included dietary recall used to calculate average fruit and vegetable intake across 3 days. All surveys were conducted on Tuesday, Wednesday, and Thursday with students recalling what they had eaten on Monday, Tuesday, and Wednesday. Each family/child was assigned an identification number, which was printed on every coupon and on each student's surveys so each child's fruit and vegetable consumption could be matched with their family's redeemed coupons.

Measurement—We collected self-reported consumption of the students using the "A Day in the Life Questionnaire" (DILQ). The DILQ has been validated for measuring incidences of fruit and vegetable intake for elementary school age children.[7] We used 1 question from the DILQ, asking children to recall what they ate for dinner. It is important to note that the DILQ gives only the frequency that fruits and vegetables were consumed, and does not assess the serving size or exact amount eaten.

All materials and procedures used in this study were approved by the University of Wisconsin-Eau Claire Institutional Review Board and the principals of both participating elementary schools.

RESULTS

Coupon Redemption

Out of 7,260 coupons, 1,981 were used for a redemption rate of 27.3%. Figure 2 presents the distribution of total coupons redeemed by families over the 4-week period. The families of 67 students (55.3%) redeemed zero coupons, while 24 families (19.8%) redeemed half or less of their coupons. Only 18 families (14.9%) redeemed more than $50 worth of coupons. On the positive side, almost $2,000 of fruits and vegetables were purchased by families, but this also means that nearly $5,300 of free fruits and vegetables were never purchased. Weekly coupon redemption rates were relatively consistent between 25% to 30% over the 4 weeks of study.

Table 1. Demographic Information

Race/Ethnicity	%
White	64.5
African American	6.6
Asian	20.7
Hispanic/Latino	5.8
American Indian	2.5
Sex	%
Male	41.3
Female	58.7

Figure 1. Example of Coupons Mailed to Participating Families

Fruit and Vegetable Intake

We compared pretest consumption to posttest consumption in weeks 2 and 4 respectively among children whose families redeemed most of the coupons (redeemers) compared to those who did not redeem any coupons (non-redeemers). Subjects were classified as "redeemers" if their family redeemed at least $14 of coupons during either week 2 or 4 during the study (N=9). These families also tended to have consistent pattern of coupon redemption. Children were classified as non-redeemers if their family did

Figure 2. Total Coupon Redemption Distribution

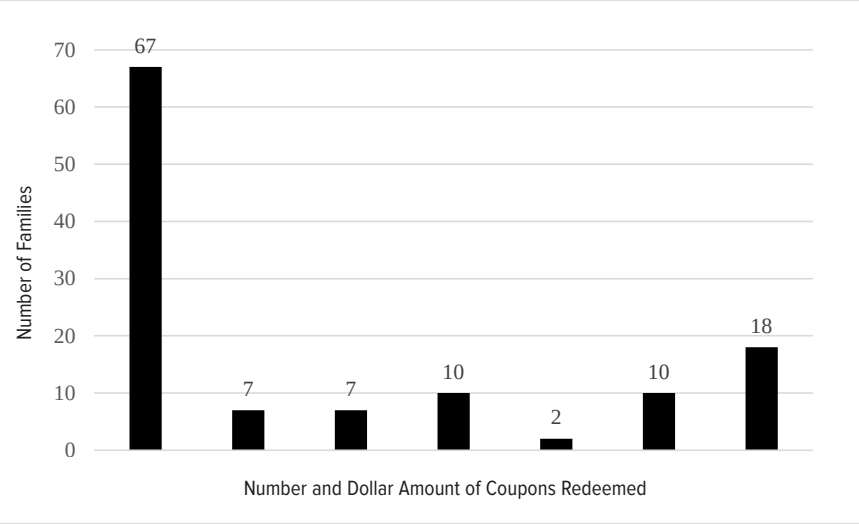

Table 2. Fruit and Vegetable Consumption

		Pretest		Posttest 1 (Week 2)		Posttest 2 (Week 4)	
		Mean	SD	Mean	SD	Mean	SD
Fruit intake	Redeemer	0.171	0.31	0.150	0.27	0.188	0.26
	Non-Redeemer	0.113	0.24	0.092	0.21	0.079	0.25
Vegetable intake	Redeemer	0.171	0.27	0.154	0.24	0.239	0.25
	Non-Redeemer	0.263	0.38	0.189	0.28	0.139	0.27

not redeem any coupons during the 4 weeks (N=67). We did not include children whose families had a random pattern of coupon redemption (some weeks high or low) in the analysis. The sample for these comparisons was restricted to only those students who were present for all 6 survey days.

Fruit Intake

The results were analyzed using a two-way 2 (redeemer vs non-redeemer) x 3 (pretest vs posttest 1 vs posttest 2) mixed design ANOVA with repeated measures on the consumption. There was a significant main effect of coupon redemption on fruit intake, F (1, 102)=3.85, *P*=.05. In general, children whose families redeemed coupons showed higher pretest fruit intake (mean=.171) than the non-redeemers (mean=.113). There was no significant change in fruit consumption among redeemers; non-redeemers showed a slight decline in their fruit intake but the difference was not significant (see Table 2).

Vegetable Intake

Vegetable intake results displayed a significant interaction between coupon redemption and the test period, F (2, 206)=4.71, *P*<.05. This indicates the change in vegetable consumption among coupon redeemers and non-redeemers. Contrast analysis revealed a significant interaction when comparing pretest and posttest 2 to coupon redemption, F (1, 103)=6.76, *P*<.01. The interaction showed that coupon redeemers consumed fewer vegetables than non-redeemers during the pretest period. However, coupon redeemers increased their vegetable intake after 4 weeks, whereas non-redeemers decreased their vegetable intake after 4 weeks suggesting that coupon redemption helps increase vegetable consumption among children (see Table 2).

DISCUSSION

This study assessed whether Wisconsin families would use free coupons to purchase fresh fruits and vegetables, and whether children in families that redeemed their coupons would increase their fruit and vegetable consumption. Despite relatively low coupon redemption rates (25%), for children whose families redeemed at least $14 of their $15 of coupons during the weeks of measurement, there was evidence of increased vegetable consumption, but not fruit consumption. For fruit consumption, the redeemers generally consumed more fruit than the non-redeemers. However, free coupons did not change the amount of fruit intake.

This study has several strengths that should be highlighted. First, the sample included 2 separate comparison groups (redeemers and non-redeemers) arising through differences in coupon use across families. Second, our design consisted of pre/post comparisons of consumption across these 2 groups with consumption measured as a 3-day average. Additionally, the children included in this study were largely from families of lower socioeconomic status and thus they represent a high-need group.

Additionally, recent changes to include fruits and vegetables in the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) food package were designed to help families meet recommended dietary intake[8] and there have also been calls to reform Supplemental Nutrition Assistance Program (SNAP) targeting healthy purchases including fruits and vegetables.[9] More investigation is needed on these topics; thus, this research has applications for both the WIC and SNAP programs.

Limitations

This study has several limitations that should be addressed in future research. The small sample size combined with a low cou-

pon redemption rate and relatively short period of study limited the power of statistical tests of the program effect. The low coupon redemption rate could be due to misunderstanding of coupon instructions, lack of knowledge/experience in buying fresh fruit and vegetables, a mismatch between coupon validity dates, or shopping patterns. Also, our consumption measure over 3 days for only dinner was not ideal, as it was possible the purchased fruits and vegetables were eaten at times other than dinner, eaten by other family members, or not eaten at all.

Future research should include all area grocery stores, including smaller stores and larger chains and use a debit card to improve redemption rates. A more effective consumption measure is also needed, possibly involving parental documentation. Additional research could also include parent follow-up surveys/focus groups to better assess factors influencing coupon redemption rates and to better understand existing barriers to increasing children's fruit and vegetable consumption.[10]

Despite these limitations, the project was successful. In 1 month, nearly $2,000 of fresh fruits and vegetables were purchased using free coupons, and vegetable consumption for dinner among children whose families used the majority of their coupons increased.

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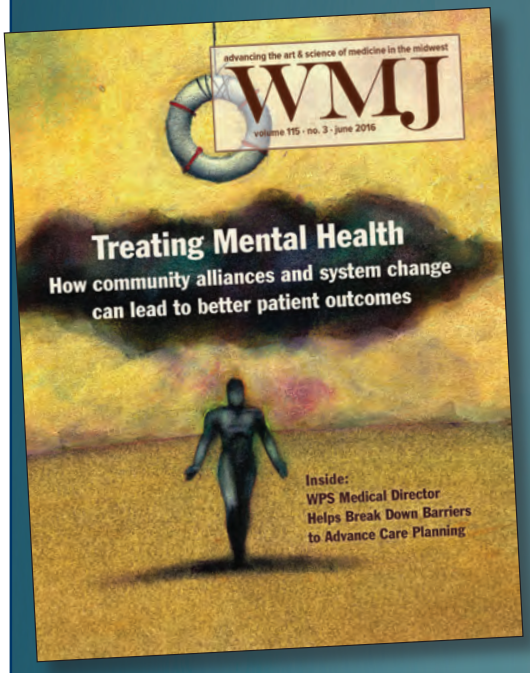

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Albee Messing, VMD, PhD

Robert N. Golden, MD

Autism in Wisconsin–Is It Increasing, and What Can We Do About It?

Albee Messing, VMD, PhD; Robert N. Golden, MD

The Waisman Center, which has graced the University of Wisconsin's west campus for more than 50 years, is internationally renowned for research and clinical services related to developmental disabilities. Named after Harry Waisman, MD, PhD, a pediatrician and biochemist who in the 1940s through 1960s pioneered work in polio and metabolic disorders, the Center has a comprehensive mission that combines clinical service, education, outreach, and research spanning the entire continuum from molecular biology to social sciences. One of a nationwide network of 14 Intellectual and Disabilities Research Centers funded by the National Institutes of Health, the Waisman Center recently received renewal of its funding through 2021 following a rigorous competitive peer-review process.

The Center achieves its clinical mission through an active partnership with UW Health, and together we manage 14 clinics and treatment programs that provide care for patients from throughout Wisconsin and the United States.

• • •

Albee Messing, VMD, PhD, is the director of the Waisman Center and a professor of neuropathology at the University of Wisconsin-Madison School of Veterinary Medicine; Robert N. Golden, MD, is dean of the UW School of Medicine and Public Health and vice chancellor for medical affairs, UW-Madison.

In this column, we highlight efforts related to autism and autism spectrum disorders (ASD). Waisman Center clinicians and researchers have been committed to advancing our understanding of these disorders for many years. Recently, public interest has increased because of an apparent rapid rise in prevalence and the corresponding burdens faced by families as well as health care and education facilities. We consider 2 questions: Is the prevalence really increasing, and how can we help children and adults affected by autism and ASD?

> Autism Spectrum Disorder should be viewed as a major national issue. For 2015, the annual combined direct medical, nonmedical, and productivity costs were estimated to be $268 billion, and the forecasted costs for 2025 will reach $461 billion.

Is the Prevalence of Autism Increasing?

One of the most notable trends in developmental disabilities in the past 2 decades has been the rising number of individuals diagnosed with autism. In 1970, Wisconsin psychiatrist Darold Treffert, MD, published the nation's first population-based study of the prevalence of autism.[1] Based on case findings throughout Wisconsin, he identified 280 children ages 3 through 12 years who met criteria for "infantile autism." This corresponded to a population prevalence of 3.1 per 10,000 children. Today, the prevalence of autism in Wisconsin and nationally is estimated to be more than 30 times higher than this, at greater than 1% of children.

To monitor the rise in autism and better understand its underlying causes, epidemiologists at the Waisman Center and the UW School of Medicine and Public Health's (SMPH) Department of Population Health Sciences have been working since 2003 with state partners, the Centers for Disease Control and Prevention in Atlanta, and other sites around the country. They have identified one clear explanation for the trend: the broadening of the concept of autism and its diagnostic criteria over time, to include a wider spectrum of impairments

in social communication and interaction with restricted and repetitive patterns of behavior. However, not all of the increase can be readily explained by the casting of a wider net of diagnostic criteria.

For example, between 2002 and 2012, a period in which there was no change in ASD diagnostic criteria, the prevalence among 8-year-old children in Wisconsin increased more than 2-fold, from 0.5% to 1.1%.[2] The rise in autism prevalence also is seen in school enrollment data. In Wisconsin, the number of children receiving special education services for autism in 2015 was 11,470—up from 20 in 1992, the first year autism was introduced as a disability category for special education. Factors contributing to the increased prevalence are complex and may include older parental age, longer interpregnancy intervals, exposure to unknown toxins, and genetic variants that will take years to understand.

How Can We Help Individuals and Families Affected by Autism and Autism Spectrum Disorders?

Although ASD is most often diagnosed in early childhood, the condition affects patients and families across the lifespan. Indeed, an ASD diagnosis has an enormous impact on patients, families, and educational, health care, and social service systems. ASD should be viewed as a major national issue. For 2015, the annual combined direct medical, nonmedical, and productivity costs were estimated to be $268 billion, and the forecasted costs for 2025 will reach $461 billion.[3] If the prevalence of ASD continues to grow at its recent pace, related costs likely will far exceed those of diabetes and attention deficit hyperactivity disorder by 2025.

In response to the increased number of patients diagnosed with ASD and the related costs, UW Health and the Waisman Center recently partnered to develop a suite of treatment programs—the "Together" series—to provide care from diagnosis to young adulthood. The goals are to reduce the patients' severity of symptoms and improve their cognitive and social skills, decrease family stressors, and, in turn, reduce the need for treatment and support as patients grow older. ASD treatment contributes to significant positive developmental changes for patients, including increases in IQ, lessening of ASD symptoms, and decreases in the amount of intervention needed at school age for patients who receive intensive early intervention.[4]

Our Starting Together Program, launched in 2016, highlights the value of early intervention for children ages 2 through 5. An in-clinic adaptation of the Early Start Denver Model (ESDM),[5] the program utilizes evidence-based practices of Applied Behavior Analysis. Sessions are provided in clinic and preschool settings, with direct one-to-one teaching and group instruction during typical preschool activities and play. Education and coaching also are provided to each family, based on the ESDM. Our goal is to develop a collection of best practices that are suitable for implementation in community settings and that are more effective than current approaches.

Even with early intervention, challenges remain. Lifespan trajectory studies identified a critical period as young adults leave the high school setting (thus leaving mandated services) and enter a period of much less-structured lifestyles. After high school, these young adults plateau and often decline in their functional capacity. To intervene in this critical period, Waisman Center investigator Leann Smith developed a multifamily group psychoeducation intervention, Transitioning Together, for adolescents with ASD and their families.[6] Outcomes from this intervention include improvements in social interactions for youth with ASD and well-being for parents. The fully manualized intervention is now available at the Waisman Center and also in dozens of schools and clinics across Wisconsin and the United States as a result of outreach and training.

UW Health and the Waisman Center share a mission to improve the lives of patients with ASD and their families through superior interdisciplinary care. This partnership provides patients with access to exemplary, evidence-based ASD treatment services that lead to the best possible clinical outcomes. We hope our ASD treatment services will serve as a model for Wisconsin, the region, and beyond.

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