

Fall, 2014



Vol: 4, Issue: Fall, 2014

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JOHNATHAN KAO

The editors of *MSRJ* are excited to announce our Fall 2014 issue, the first issue of the new academic year. We have been overwhelmed with amazing articles from medical students around the world and this has allowed us to publish our largest issue yet! This issue includes stimulating articles written by students from the University of Toronto, Creighton University School of Medicine, Saba University School of Medicine, Michigan State University College of Osteopathic Medicine, and Michigan State University College of Human Medicine.

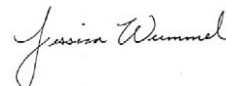
Since the release of our last issue, we are delighted to announce the winners of our submission contest! Throughout the last year, *MSRJ* has been carefully reviewing articles submitted to our contest looking for winners in the following categories: Best Original Research, Best Case Report, Best Review, and Best Reflection. Our winners include Zach Jarou and colleagues for their submission of "Public Stroke Knowledge – Those Most at Risk, Least Able to Identify Symptoms" for Best Original Research; Victoria Stahl and colleagues for their article, "Morphine Induced Myoclonus in a Patient with End-Stage Renal Disease" for Best Case Report; Catalina Dumitrascu for her submission of "Substance Abuse among Physicians and Medical Students," for Best Review; and Alec Beaney's "Future Medical Practice and Genetics," for Best Reflection. Our staff were amazed by the quality of submissions we received and were happy to publish the majority of the submissions despite only being able to give a few awards. The winners of this contest each received a \$300 scholarship and are featured in a special post on our website. We were very pleased with the result of this contest and are thinking about making it a recurring event! We encourage our readers to stay tuned for the next submission dates and contest information.

The journal has great plans for this upcoming year. We plan on continuing to review and publish the wonderful submissions we receive. We also plan on reaching out to other medical schools to see how we can broaden our reach and involvement with our journal. We continue to receive requests to speak at various functions to inform students how to publish their hard work as well as inquiries into how students can become involved with us. We are excited at the prospect of involving other students into our operations. Our staff will also be looking into other research conferences to attend and promote our journal as another publishing option.

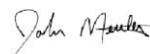
Also new to *MSRJ* is the addition of many new staff members! Our staff have nearly doubled in size since our last issue. Our student elective continues to be a great success in recruiting motivated students to join our staff. This new batch of students has already proven to be incredibly hard working with great ideas, and we are excited to see where the journal goes with their assistance and expertise. After our Spring issue, our Executive Editor, Kevin Patterson graduated and went on to start his Internal Medicine residency at Ohio State University. We would like to thank him for his hard work with *MSRJ* and acknowledge all the progress he allowed the journal to make, including but not limited to increasing the journal's indexing, spearheading our submission contest, and adding medical student education to our publication process. The leadership of the journal this year includes Jessica Wummel and Jack Mettler, both fourth-year students at MSU College of Human Medicine. Jessica was Executive Editor last year and an *MSRJ* editor since her matriculation into medical school. She is excited to continue leading the journal and to be joined by Jack, an *MSRJ* editor since his first medical school year, as well. They are both looking forward to continuing Kevin's legacy and making one of their own.

As always, we would like to thank the Michigan State University College of Human Medicine for their continued support. In addition, we would like to acknowledge the hard work of our talented staff in making this issue possible; without them, this journal's success would not be where it is today. We hope that our readers will continue to follow the progress of the *MSRJ* both on Facebook and Twitter, and on our website at <http://www.MSRJ.org>. Please continue sending your manuscripts to us; we are always excited to read the amazing work from our fellow students.

Sincerely,



Jessica Wummel
Executive Editor – MSRJ 2014–2015



Jack Mettler
Executive Editor – MSRJ 2014–2015



Broken

Timothy DeKoninck*

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There are several elements symbolized in the mosaic that represent a doctor–patient relationship. This work strives to piece together, and serve as a reminder of, the elements that make for a successful and impactful relationship.

Multiple pieces of tile: The pieces of tile in the mosaic are used to depict the compilation of various elements that contribute to the personhood of both the patient and their doctor. Both are made up of a variety of different cultural, experiential, familial and personal elements. These elements, though similar at first glance, are highly unique, and they directly influence how patients perceive their diseases and how doctors recognize the illnesses.

Brokenness: The ‘brokenness’ in the medium is used to illustrate how both the doctor and the patient are ‘broken’ people. The brokenness of the tile is also a representation of the Michigan State University College of Human Medicine (CHM) virtue of humility, as doctors appreciate the limitations of their own mental, social and physical abilities. It also provides a beautiful picture of how medical students are broken down and

reassembled in the process of medical education, demonstrating the transition from a functional individual element of society, represented by the tile and media choice, to an integrated part of a grand picture of humanistic medicine, represented by the mosaic.

Power and position: The picture of the patient portrayed as a young child depicts the element of mercy in the doctor–patient relationship as an embodiment of the CHM virtue to meet the needs of the patient regardless of the perceived position of power that the doctor may hold. The doctor is also on the same eye level as the patient, being actively engaged and closing the power divide. The choice of a child, who fills one of the most vulnerable positions of society, to depict the patient portrays how many patients may feel when bringing his or her health concerns before a doctor. The doctor in this picture assumes the responsibility to oversee the care of this patient, to serve as an advocate for the patient’s rights and to echo and amplify the voice of their patient.

Medical imagery: The choice of a stethoscope as the tool for diagnosis and the image of a small-sized heart

in the ear of the doctor depicts the importance of the doctor 'listening' to not only what is present in the patient physically but also hearing what is going on emotionally, with the heart as a picture of the soul – the biopsychosocial framework – of the patient.

Heart symbolism: The heart in this piece also symbolizes love and compassion that must be present in a

doctor–patient relationship. The heart in the ear of the doctor also embodies the patient-centered approach to first listen to the patients and then encourage them to voice their concerns. The size of the heart in the child relative to the size of the heart in the doctor depicts how the patient may perceive his or her disease differently from that of the physician.

A Review of the Psychological and Emotional Issues in Men with Prostate Cancer and their Partners

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Keywords: *sexual health; relationships; intimacy; radiotherapy; psycho-supportive treatment; hormone therapy.*

INTRODUCTION

Howard L. Harrod on his struggles with prostate cancer (PCa): 'Not only had I a sense of having been mutilated, but I had lost the very capacities that were symbolically associated with manhood.'¹ Many patients with PCa experience this jolt to their sense of manhood, thus making PCa unique among the various cancer diagnoses and worthy of independent discussion. In addition, PCa remains the most common male cancer and the third leading cause of all male cancer deaths.² Most physicians are aware of the link between cancer and mental health issues, but many forget or overlook just how important it is to address a patient's state of mental health. The overall prevalence of depression in those with PCa has been reported to be between 14 and 22% depending on treatment stage (pre, during, and post).³ Depression/anxiety and PCa are associated with a nearly fivefold increased risk of Emergency Room (ER) visits, nearly threefold increased risk of hospitalization, and a threefold increased risk of excess death compared to those without mental health issues.⁴ Furthermore, patients suffering from mental health issues are less likely to adhere to treatment, and are more likely to experience adverse reactions to treatment.³ Lastly, depression and other mental health issues may be exceedingly difficult to identify and treat in males, thus many cases may go undiagnosed and either untreated or undertreated.⁵ Ultimately, PCa and mental health issues may lead to an overall increase in medical costs and poor patient outcomes. Therefore, this reflection piece will serve to highlight the important relationship between PCa and mental health and provide an update on available treatments to support patients with PCa and their families.

SEXUAL AND EMOTIONAL EFFECTS OF DIAGNOSIS

PCa, from beginning to end, screening to death, is a disease riddled with psychological and emotional torment. Zisman et al, in a study on prostate biopsies, a procedure utilized in the diagnosis of PCa, reported nearly two-thirds of patients experience significant amounts of anxiety both before and up to 7 days after the biopsy.⁶ Additionally, acute sexual dysfunction, lasting up to 30 days, was reported in 10% of patients. These findings were likely related to the psychological effects of worry and/or the physical effects of the biopsy itself. At diagnosis, thoughts and feelings involving fear of cancer spread, concern for loved ones, and impact on sexual health lead to a near immediate adverse impact on patient psyche.⁷ Those most adversely impacted (and why) are those less than 65 years of age (decreased sexual functioning, greater pain, sleep disturbances, uncomfortable becoming sexually intimate), those diagnosed within the past year (fatigue, frequent urination, sleep disturbances, and hot flushes), and/or those with metastatic disease (depression, anxiety).⁷ In addition, the stigma of having cancer, and potentially impaired sexuality, may prevent these patients from seeking adequate social and psychological support which may lead to a continual deterioration of mental health.⁸ PCa itself may lead to psychological and emotional issues, but what about its treatment?

SEXUAL AND EMOTIONAL EFFECTS OF PCa TREATMENT

Active surveillance involves monitoring overall disease progression through repeat prostate-specific antigen (PSA) testing, digital rectal exams, and biopsies, but involves no active therapy. Though the therapy is

physically less altering, it is still associated with sexual dysfunction, distress, depression, and anxiety.⁹ It has been hypothesized these issues may be related to biopsies (mentioned previously), distress over disease, psychological symptoms caused by cancer itself, or by the burden of age.⁹ Regardless of cause, physicians should be aware that the mere presence of cancer, regardless of severity, is psychologically disturbing and should be addressed.

Active treatments include hormonal therapy, radiotherapy, and radical prostatectomy. Hormonal therapy involves giving medication to suppress testicular androgen production and subsequently reduce testosterone, PSA, and prostate tumor volume.¹⁰ Of all PCa treatments, hormone therapy has the potential to cause the most physical, psychological, and emotional issues.¹¹ Physically, patients experience loss of muscle and bone mass, fat redistribution, increased risk of osteoporosis, diabetes, obesity, and cardiovascular-related mortality.¹⁰ In addition, they experience loss of libido, erectile dysfunction, hot flashes, and cognitive dysfunction. In all, psychological and emotional issues may arise including depression, anxiety, fatigue, irritability, moodiness, tension, anxiety, and loss of vigor.¹⁰

Alternatively, radiotherapy, which involves applying high doses of ionizing radiation to the prostate and surrounding tissue in order to control, kill, or shrink malignant cells, may have the least overall impact on patient mental health. Of those that experience mental health issues most are related to the side effects of treatment and include severe lower urinary tracts symptoms (20%), sexual dysfunction (50%), fatigue, social dysfunction, sleep disturbances, cognitive dysfunction, gastrointestinal issues (13–38%), and a moderate to severe impairment in quality of life (9%).¹² In reality, a small but significant number of patients may go on to experience anxiety, depression, embarrassment, shame, anger, guilt, intimacy issues, and partner conflict.

The most established PCa treatment, radical prostatectomy, is described as the surgical removal of the entire prostate gland, seminal vesicles, ampulla of the vas deferens, and possibly lymph nodes. Mental health issues related to this treatment involve impaired erectile function, sexual desire, and sexual satisfaction.¹³ The nerves involved in obtaining and maintaining erections are intimately involved with the prostate, and although preservation may be attempted, sexual function is rarely the same pre- to postsurgery. It has been reported that approximately 60% of patients are moderately to extremely dissatisfied with their impaired sexual function.¹³ Those most likely to suffer from impaired sexual

function, and the depression, anxiety, embarrassment, shame, guilt, intimacy issues, and partner conflict that may follow, are those that maintain high levels of sexual desire but have limited sexual function.¹³ Ultimately, active PCa treatment appears to be a major cause of mental health issues, and in order to ensure proper patient care, physicians, regardless of specialty, should address these issues.

SEXUAL AND EMOTIONAL EFFECTS OF PCa ON SIGNIFICANT OTHERS

The discussion thus far has centered on patients and their psychological and emotional issues related to PCa and its treatment. For many patients, there is a significant other who may experience similar issues. Partner issues are seldom addressed because physicians often forget disease affects families, not individuals. Few papers have studied the role of the partner and the psychological and emotional issues partners face following a PCa diagnosis in their significant other. In general, psychological and emotional issues related to cancer diagnosis stem from four domains: the delivery of instrumental care, the emotional challenge of suffering, altered access to their partner, and altered intimacy with their partner.¹⁴ A paper by Couper et al, on PCa diagnosis and the effects of treatment on female partners, reported many partners have maladaptive coping patterns including avoidance, wishful-thinking, and self-blame, and the severity of these maladaptive coping patterns corresponds directly with their degree of psychological distress (adjustment disorders, anxiety, depression, anger, etc.).¹⁵ They also reported a large proportion of these women experience levels of distress that surpasses the threshold for psychiatric diagnosis. Kornblith et al, in a cross-sectional PCa study, discovered spouses report significantly greater psychological distress than the patients themselves.¹⁶ Finally, JW Couper reported that in the first 6 months following a PCa diagnosis partner-reported marital satisfaction scores decrease and continue to do so as the relationship continues.¹⁷ Ultimately, partners are important sources of support for cancer patients. To maintain this support structure, it is critical physicians address their well-being.

PREVENTION AND TREATMENT OF PCa-RELATED PSYCHOLOGICAL AND EMOTIONAL ISSUES

A common PCa theme is sexual dysfunction (not only in patients, but their partners as well). A survey conducted by Singer et al reported that two-thirds of men were willing to accept a 10% decrease in overall 5-year

survival (from 90 to 80%) to improve their chance of sexual potency following PCa treatment.¹⁸ Furthermore, a study by Tavlarides et al reported that as anxiety levels increase, both sexual dysfunction and depression levels significantly increase.¹⁹ Therefore, it is not surprising a majority of PCa-related mental health issues are associated with the fear/actual loss of sexual potency. Treatment of sexual potency issues may help prevent/treat mental health issues. Penile rehabilitation therapy involves a combination of therapies including phosphodiesterase-5 inhibitors (sildenafil), intracavernosal injections (alprostadil), vacuum constriction devices, and penile prosthesis, but efficacy remains widely variable.²⁰ Ultimately, studies have yet to be conducted regarding treatment of sexual dysfunction and its effect on depression/anxiety. It can be reasonably hypothesized, however, that improvement in potency would lead to improvement in mental health of both patients with PCa and their partners.

What else can be done to prevent/treat mental health issues related to PCa? Regardless of the disease process or treatment, the simplest and most effective thing a physician can do is to foster a supportive relationship and to simply ask patients how they are doing at each visit. This initial screening allows physicians to triage and treat minor issues in-office or refer out for specialized care if necessary. It is especially important to ask patients about suicide, as risk of suicide in men with PCa is fourfold higher than that of their age-matched peers (incidence 55 vs. 274 per 100 k).²¹ Beyond in-office discussion, support, and the prescribing of medication, exist a number of psycho-supportive treatments for patients and their struggling partners. Mental health specialists often deliver these treatments, but all physicians should be familiar with the psycho-supportive treatments available as this allows for proper referral. For individuals, these psycho-supportive treatments include: cognitive behavioral therapy (CBT) (traditional and with physical activity), psychoeducational therapy (lecture, question, discussion groups), and hypnosis.

A meta-analysis by Dale et al reported CBT provided the most substantial benefit.²² It is consistently more effective in regards to improving quality of life and sexual function, and in decreasing depression, anxiety, psychological distress, fatigue, physical impairment, and pain. Hypnosis was associated with highly significant improvements in anxiety, depression, and psychological distress. Finally, psychoeducational therapies had mixed results and were least successful.

Another type of therapy, considered most important of all, is psycho-supportive treatment that cares for both the individual with the disease and his partner. It is important because marital status has been shown to be an independent predictor of overall mortality in men with PCa, and unmarried men have a higher risk of PCa-specific mortality.²³ As mentioned previously, few papers discuss partners' psychological and emotional issues, but fewer discuss strategies to treat them. The only treatment successfully employed for couples is couple-focused psychosocial intervention (couples CBT).¹⁷ This treatment is backed by years of data in breast cancer patients and their male partners, but few data exist on its effectiveness in relation to PCa patients and their female partners.¹⁷ Despite the lack of an evidence-based approach, most agree preventative, couple-focused intervention would likely be beneficial to the patient and his partner.¹⁵

CONCLUSION

Overall, psychological and emotional issues including depression, anxiety, fear, anger, shame, embarrassment, and loss of intimacy are associated with PCa. Further studies investigating the relationship between PCa outcomes, sexual function, and mental health are required to fully assess these issues. Ultimately, physicians have the responsibility to inquire about these issues and to offer treatment if able or to refer patients to more specialized providers. Remember that cancer affects both individuals and their partners, and steps must be taken to provide physical, mental, and emotional treatment and support for all.

Conflict of interest and funding: The author has not received any funding or benefits from industry or elsewhere to conduct this study.

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Acute Bronchiolitis – Case Report and Review of Management Guidelines

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Introduction: *The treatment of acute bronchiolitis is controversial, despite the fact that several well-designed trials have been conducted on the subject.*

Patient profile: *A 10-month-old boy presented to the emergency department with a 3-day history of upper respiratory tract symptoms and an expiratory wheeze. Chest X-ray showed right upper lobe atelectasis. He was diagnosed with acute bronchiolitis.*

Interventions: *He received nebulized salbutamol (albuterol) and oral dexamethasone in the emergency department. He was admitted to hospital overnight for continued salbutamol treatment via a metered-dose inhaler.*

Discussion: *Five main treatment regimens exist for acute bronchiolitis – nebulized epinephrine (adrenaline), other bronchodilators, nebulized hypertonic saline, glucocorticoids, and combinations of these. Nebulized epinephrine decreases the rate of hospitalization, other bronchodilators improve symptoms, and nebulized hypertonic saline reduces the length of hospitalization. There is no strong evidence for glucocorticoids or combinations of these treatments. Combined treatment with epinephrine and dexamethasone reduces rate of hospitalization.*

Keywords: *bronchiolitis; case reports; pediatrics; practice guideline; therapeutics.*

INTRODUCTION AND PATIENT PROFILE

Acute bronchiolitis, caused by respiratory syncytial virus (RSV) in approximately 50–80% of cases, is a viral infection of the lower respiratory tract mostly affecting the bronchioles.¹ Other causative viruses include human metapneumovirus, parainfluenza, influenza, and rhinovirus, and in approximately 10–30% of cases more than one virus is involved.¹ It typically presents with viral upper respiratory infection symptoms followed by wheezing and increased work of breathing, and it occurs in children younger than age 2.¹ This report serves as a teaching case describing a common presentation of acute bronchiolitis, and the subsequent discussion provides an overview of the evidence for different treatment options.

A 10-month-old boy presented to the emergency department with a 3-day history of wet cough and congestion. His mother brought him in because of increased work of breathing, noisy breathing, and a fever for the last 2 days. There was no clear history of sick contacts; however, he had recently started attending daycare. He was previously well, and his immunizations were up to date. His only medication was vitamin D drops, and he had no known allergies. Obstetrical history was unremarkable. He had a family history of

atopy, as his mother had hay fever and his father had childhood asthma.

At triage in the emergency department his oxygen saturation was 92% on room air and he displayed increased work of breathing, with subcostal and intercostal retractions with inspiration. He was audibly wheezing on expiration. On auscultation, he had significant expiratory wheezing bilaterally and decreased air entry to the right upper lobe.

Chest PA and lateral X-rays were taken (Figs. 1 and 2). Three possible interpretations were discussed: right upper lobe collapse (atelectasis), right upper lobe pneumonia, and thymus displaced from the center due to rotation/poor positioning of the patient during the X-ray. It was decided that the image likely demonstrated right upper lobe collapse, since there was a complete opacity and there was upward hilar retraction ipsilaterally. The most likely etiology of the lobar collapse was a mucus plug.

INTERVENTIONS AND OUTCOMES

After three nebulized salbutamol (albuterol) treatments in the emergency department his oxygen saturation improved to 95% on room air. He also received a

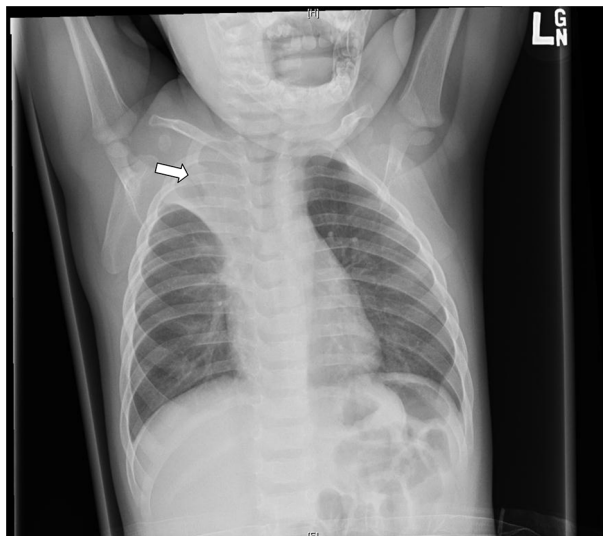


Figure 1. PA chest X-ray. Note the opacity in the right upper lobe (arrow).

dose of oral dexamethasone. On examination after these treatments, he appeared generally well and was in no acute respiratory distress. He continued to have mild substernal retractions with inspiration. However, there were no intercostal retractions or tracheal tug. His wheeze was less audible; however, on auscultation wheezing was still heard bilaterally. He continued to have decreased air entry in the right upper lobe.

The patient was admitted to hospital for continued salbutamol treatment via a metered-dose inhaler (MDI)

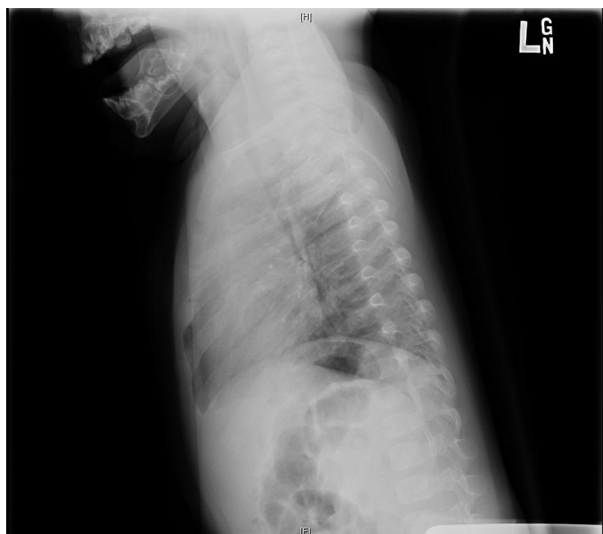


Figure 2. Lateral chest X-ray. The opacity in the upper lung field is also seen in the lateral view.

and supportive management. After one night in hospital his work of breathing decreased, his wheeze was no longer present, and he was eating and drinking well. Salbutamol was discontinued and his symptoms did not return, so he was discharged home with appropriate follow-up for his right upper lobe collapse. The RSV nasopharyngeal swab taken in the emergency department came back negative on the day of discharge.

DISCUSSION

Acute bronchiolitis is a common condition, and a common reason for emergency department visits for children under the age of two. However, management of this condition can be highly variable, as no clear treatment guidelines exist despite several well-designed trials and meta-analyses having been performed. Five main management principles exist; however, there are many treatment options.

Nebulized epinephrine (adrenaline) has been shown to reduce admissions to hospital on the day of presentation and to improve short-term clinical scores.² However, there is no strong evidence that epinephrine reduces the length of stay among patients admitted with bronchiolitis.^{2,3} Other bronchodilators such as salbutamol and ipratropium bromide alone have not been reliably shown to reduce the rate or the length of hospitalization for acute bronchiolitis.⁴ They may, however, temporarily improve symptoms.⁴ Additionally, it is not always possible to be certain that a child is presenting with bronchiolitis, since it is primarily a clinical diagnosis and other conditions such as reactive airways or asthma can present very similarly. When assessing the patient it is important to determine if there is a personal or family history of atopy. If so the likelihood of asthma increases, and one can consider administering a bronchodilator such as salbutamol in addition to oral or inhaled steroids even if bronchiolitis is still the most likely diagnosis. This is how our patient was treated due to his family history of atopy; however, bronchiolitis was the more common diagnosis due to the presence of fever.

For non-severe acute bronchiolitis, nebulized hypertonic saline (3% and possibly 5%) has been shown to reduce the length of hospitalization.⁵ Glucocorticoids alone have not been reliably shown to reduce the rate or the length of hospitalization for acute bronchiolitis.⁶

The pathophysiology in bronchiolitis leading to airway obstruction and breathing difficulties is multifaceted. Underlying processes include inflammation, mucous plugging, and bronchospasm.⁷ Therefore, it makes sense that combining treatments which alleviate

different components of the overall pathophysiology could be superior to any single treatment. Unfortunately, not many strong trials have specifically looked at combination regimens for the treatment of acute bronchiolitis. One large, well-designed randomized controlled trial reported that patients presenting to the emergency department with bronchiolitis who were treated with both epinephrine and dexamethasone had a decreased rate of admission to hospital over the week following their initial presentation to the emergency department.⁸

In addition to the five treatment regimens discussed, another common approach is to limit treatment to supportive care, including supplemental oxygen, fluids, and antipyretics as necessary. These treatments are given to all children with bronchiolitis in addition to any of the treatments mentioned thus far. Bronchiolitis is fundamentally a self-limited condition, and more aggressive management should be reserved for cases with advanced symptoms such as significant respiratory distress.

Other management principles being investigated include nebulized deoxyribonuclease,⁹ chest physiotherapy,¹⁰ high-flow nasal cannula therapy,¹¹ and steam inhalation or humidified oxygen.¹² For each of these treatments, there is either insufficient evidence of effectiveness or good evidence of ineffectiveness in the management of bronchiolitis. Heliox (helium and oxygen mixture) inhalation therapy may temporarily reduce respiratory symptoms among infants admitted to an intensive care unit with respiratory distress.¹³ As bronchiolitis is caused by a viral infection, it does not intuitively make sense to routinely include antibiotics in the treatment, and studies support this.¹⁴ However, in the subset of patients who have a superimposed bacterial infection or secondary respiratory failure, antibiotics are indicated, in keeping with standard treatment of these conditions. In addition, children at increased risk for significant morbidity due to RSV, such as severely premature infants and infants with certain heart and lung conditions, can receive palivizumab, a monoclonal antibody against the RSV virus, to prevent infections.¹⁵

KEY LEARNING POINTS

1. Acute bronchiolitis is a common pediatric condition, affecting approximately 15% of infants in the first year of life. It is diagnosed clinically and presents with wheezing, upper respiratory tract infectious symptoms, and increased respiratory effort, typically in children younger than 2 years of age. It often presents similarly as reactive airway syndrome, general viral upper respiratory tract infections, and viral-induced asthma. It is most common in the winter months, coinciding with when the causative viruses are more prevalent.
2. The course of acute bronchiolitis is generally mild and self-limited; however, complications can occur and severe cases often require hospitalization.
3. There is no single universally recommended treatment for acute bronchiolitis. Epinephrine with and without dexamethasone decreases hospital admissions, bronchodilators decrease symptoms, and hypertonic saline decreases length of hospital stay.

Conflicts of interest and funding: The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

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Sebaceous Carcinoma of the Abdominal Wall: A Potential Indicator of Muir–Torre Syndrome

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Introduction: Sebaceous carcinoma is a rare dermatologic tumor affecting the pilosebaceous apparatus of the skin. While the majority of sebaceous carcinomas arise from sebaceous glands in the ocular area, extraocular sebaceous carcinomas, arising from any region populated with sebaceous glands have also been reported. Sebaceous carcinoma can present as a single lesion or in association with secondary malignancies, most commonly with those found in Muir–Torre syndrome (MTS), an autosomal dominant condition associated with several types of sebaceous neoplasms as well as a variety of visceral malignancies. The most common form of MTS has been described as a variant of hereditary non-polyposis colorectal cancer (Lynch syndrome).

Patient profile: Here, we describe the case of a 55-year-old male, with a known history of colorectal cancer, presenting with a rapidly enlarging abdominal wall mass.

Interventions and outcomes: Surgical excision of the mass histologically demonstrated sebaceous carcinoma. This diagnosis, the incidental discovery of a papillary thyroid carcinoma and the patient's history of colorectal cancer, prompted referral for genetic counseling, the results of which are still pending.

Discussion: Sebaceous carcinoma is one of several diagnostic criteria of MTS and its presence should prompt a complete evaluation for underlying internal malignancies.

Keywords: sebaceous gland; sebaceous carcinoma; abdominal wall; Muir–Torre syndrome; colorectal cancer; HNPCC.

INTRODUCTION

Sebaceous glands, found most abundantly in the skin of the head and neck, are exocrine glands arising from the epidermis and epidermal appendages. These oil-producing glands secrete sebum, a mixture of lipids and cellular debris, into the hair follicle to reduce evaporation from the epidermal surface. The ocular region has a high density of sebaceous glands, including the modified Zeis glands of the cilia and meibomian glands of the eyelid.¹ While the head and neck are the most populated areas, sebaceous glands are found on any hair-bearing regions of the body.

Sebaceous carcinoma is a rare tumor affecting the sebaceous glands. These tumors are classified as ocular or extraocular, depending on the involvement of the eyelid structures. Seventy-five percent of sebaceous carcinomas are ocular, most commonly arising from the meibomian glands, while 25% are extraocular, arising from any region populated with sebaceous glands.¹ While sebaceous carcinoma can present as a single lesion, it is frequently associated with secondary malignancies, most commonly those found in Muir–Torre syndrome (MTS). MTS is an autosomal dominant condition associated with sebaceous neoplasms, keratoacanthomas

and a variety of visceral malignancies, including colorectal, endometrial and urological.² While MTS can arise in individuals without a family history, it has a prominent familial association; the most common type of MTS is considered a variant of hereditary non-polyposis colorectal cancer (HNPCC, Lynch syndrome), a genetic condition characterized by defects in DNA mismatch repair genes. While both the MLH1 and MSH2 genes are mutated in HNPCC, mutations in MSH2 are more frequently reported in cases of MTS.^{3,4} Sebaceous carcinoma is often considered a potential diagnostic sign of MTS⁴ (Table 1), and its presence should prompt a complete evaluation for gastrointestinal and genitourinary cancers. Due to its inheritance pattern, relatives of patients diagnosed with MTS should also be examined for sebaceous and visceral malignancies.⁵

PATIENT PROFILE

The patient was a 55-year-old Caucasian male presenting with a 5-year history of a non-painful abdominal wall mass that had been rapidly increasing in size over the past year. He denied any erythema or drainage from the lesion; however, he did note a 10–20

Table 1. Diagnostic criteria for Muir–Torre syndrome

Group A

- 1) Sebaceous adenoma
- 2) Sebaceous epithelioma
- 3) Sebaceous carcinoma
- 4) Keratoacanthoma with sebaceous differentiation

Group B

- 1) Visceral malignancy

Group C

- 1) Multiple keratoacanthomas
- 2) Multiple visceral malignancies
- 3) Family history of Muir–Torre syndrome

Diagnosis requires one criterion from Group A and Group B, or all three from Group C.

From Ref. (4).

pound weight loss over the past year. The patient's past medical history was significant for colorectal cancer (T4N0) diagnosed approximately 16 years prior to the date of presentation. This was treated with subtotal colectomy and partial cystectomy along with adjuvant chemotherapy. A basal cell carcinoma of the nose and keratoacanthoma had been locally excised prior to presentation. The patient's father had a history of gallbladder cancer; however, the rest of the family history and social history were unremarkable. On physical examination of the neck, a 1 cm mobile, non-tender nodule was palpated at the angle of the left mandible; no goiter was noted. An 8 × 8 cm, mobile, non-tender firm mass was located over the right mid-abdomen; the mass elevated the skin but did not demonstrate any drainage or erythema. The abdomen was found to be soft, non-tender and non-distended.

INTERVENTIONS AND OUTCOME

The patient underwent an extensive diagnostic workup to determine the source of the abdominal wall lesion. A core needle biopsy of the abdominal wall mass was performed, with pathology of the specimen demonstrating carcinoma with extensive necrosis, suggestive of an urothelial primary source. Due to the patient's history of colorectal carcinoma, a carcinoembryonic antigen (CEA) blood level and flexible sigmoidoscopy were also completed at this time, both with normal results. A CT scan of the abdomen (Fig. 1) demonstrated a solitary, heterogeneous mass of the right abdominal wall with a distinct fat plane between the mass and anterior rectus fascia. Due to the unexpected urothelial tumor markers, a PET CT was performed to determine the site of the primary lesion. This demonstrated hypermetabolic regions in both the anterior abdominal

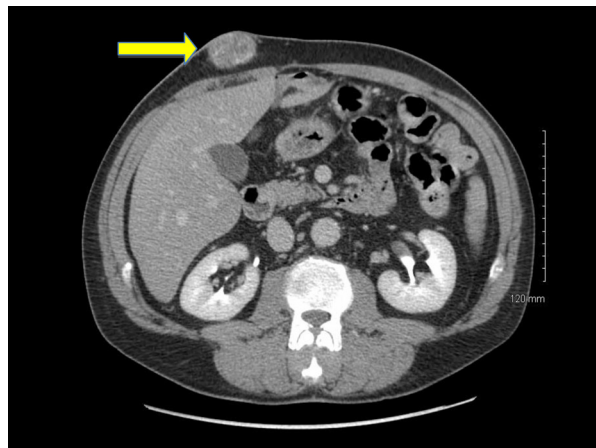


Figure 1. CT scan demonstrating a solitary, heterogeneous 6 × 4 cm mass of the right abdominal wall (arrow) with a distinct fat plane overlying the anterior rectus fascia. Diagnosis of sebaceous carcinoma was made upon surgical excision.

wall as well as a left thyroid nodule; there was no evidence of distant metastatic disease. Ultrasound guided biopsy of the left thyroid nodule was suggestive of papillary thyroid carcinoma, while the mandibular mass found on physical exam was benign. At that time, the patient was referred to urology due to the possibility of a primary urothelial source; however, cystoscopy with FISH analysis was negative for evidence of urothelial carcinoma.

Despite an extensive workup, the etiology of the mass was still unclear, so the patient was taken to the operating room for a wide local excision. A 6 × 4 cm mass with 1 cm margins was removed, and it demonstrated a focally hemorrhagic sebaceous carcinoma with clear margins. The patient returned for a total thyroidectomy where a 1.7 × 1.4 × 1.2 cm solid nodule, consistent with papillary thyroid carcinoma, was removed. Due to his history of visceral malignancy and diagnostic workup uncovering both sebaceous and internal malignancies, the patient was referred for genetic counseling. At the time of this article's publication, the results of the patient's genetic tests are still pending.

DISCUSSION

Extraocular sebaceous carcinomas, although rare, are most likely to arise from the skin of the head and neck. Less commonly involved regions include the extremities and external genitalia.¹ Lesions are clinically described as painless, yellow to pink, slowly enlarging, subcutaneous nodules; ulceration and bleeding are

rare secondary changes.⁶ Incidence of the lesion is generally slightly higher in male patients, with a median age of diagnosis of 73 years.⁷ A review of the literature suggests that ocular and extraocular sebaceous carcinomas share a similar prognosis. A number of metastatic cases of both types have been reported and must be monitored for.⁷

In patients presenting with a sebaceous neoplasm, the diagnosis of MTS requires at least one associated visceral malignancy. While sebaceous carcinoma is not as specific a marker for MTS as a sebaceous adenoma, it has been reported in at least 29 patients with MTS and is considered a possible marker of the syndrome.⁴ Thus, the presence of any sebaceous tumor warrants a search for internal malignancy, as well as MTS. According to a review by Cohen et al, the most commonly associated visceral neoplasms in MTS are colorectal (51%) and genitourinary (25%); cutaneous lesions may occur before or concurrently with the diagnosis of visceral malignancies.⁵

Although the results of genetic testing of the patient discussed in this report were still pending at the time of publication, his diagnosis of sebaceous carcinoma along with his history of multiple internal malignancies suggests a possible case of MTS. We recommended regular follow-up and routine monitoring of both the patient and his family members; this includes regular screening for colorectal cancer as well as annual dermatologic examinations. This case demonstrated the complex diagnostic workup that may be required in patients with multiple malignancies suggestive of MTS. In the future, an earlier suspicion for MTS in similar patients may prompt a more efficient diagnostic process.

Sebaceous neoplasms, especially in extraocular regions, often mimic more benign cystic lesions leading to misdiagnosis. While the majority of patients will be discovered to have benign lesions, this case demonstrates the importance of obtaining an accurate diagnosis, as sebaceous carcinoma may be an important clue to underlying visceral malignancies associated with MTS.

LEARNING POINTS

1. Seventy-five percent of sebaceous carcinomas are ocular, while 25% are extraocular, arising from any hair-bearing region of the body.

2. Sebaceous carcinoma is commonly associated with MTS, an autosomal dominant condition considered a variant of HNPCC (Lynch) syndrome.
3. In patients presenting with a sebaceous neoplasm, the diagnosis of MTS requires at least one associated visceral malignancy, most commonly colorectal, genitourinary or endometrial.
4. Sebaceous carcinoma is considered a potential diagnostic sign of MTS and its presence should prompt a complete evaluation for internal malignancies, including colorectal cancer screening and annual dermatologic exams.
5. Due to its inheritance pattern, relatives of patients diagnosed with MTS should also be examined for sebaceous and visceral malignancies.

Conflict of interest and funding: The author has not received any funding or benefits from industry or elsewhere to conduct this study.

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A Case of Severe, Refractory Antipsychotic-Induced Orthostatic Hypotension

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Introduction: Antipsychotics have many adverse effects including orthostatic hypotension. Orthostatic hypotension is ideally treated with non-pharmacological strategies; however, these often fail leading to utilization of pharmacological methods. Currently, there is no agreed upon management or protocol for addressing antipsychotic-induced orthostatic hypotension and research in this area is limited.

Patient profile: A 60-year-old man with a long history of schizophrenia who was receiving Haldol[®] Deconoate 200 mg injections every 4 weeks due to previous non-compliance. He was admitted to the inpatient psychiatric service due to worsening psychosis and suicidal behavior.

Intervention: Despite use of medications, the patient was switched to risperidone with a goal of transition to an atypical long-acting injectable. The psychosis improved, but the patient developed orthostatic hypotension. After his medications were held, his blood pressure continued to be grossly abnormal. A number of different tests were completed followed by standard non-pharmacological treatment, which proved unsuccessful. Despite receiving intravenous fluid boluses to maintain his blood pressure, the patient required pharmacological treatment. This included midodrine and fludrocortisone, and concluded with Adderall[®] as his blood pressure stabilized.

Conclusion: This case of a 60-year-old man with antipsychotic-induced orthostatic hypotension elucidates the frustration healthcare professionals and patients face with this common treatment-resistant condition. A treatment algorithm for managing drug-induced orthostatic hypotension is proposed and is a nidus for development of future protocols.

Keywords: orthostatic hypotension; antipsychotics; refractory; side effects; schizophrenia; management guidelines

INTRODUCTION AND PATIENT PROFILE

Compliance with antipsychotic medications is poor given the high degree of intolerability of the adverse effects. Mackin indicates that the most common adverse autonomic side effect of antipsychotics is orthostatic hypotension.¹ Alpha-1 adrenergic receptor antagonism has been shown to play a key role in this mechanism.²⁻⁴ Dosages are often limited and medications switched to avoid continued hypotensive episodes. Orthostatic hypotension is ideally treated with non-pharmacological strategies; however, these often fail and use of alpha agonists has become a first-line treatment for resistant orthostatic hypotension.⁴ Although the use of midodrine and other medications is not new, little is known about their effectiveness with antipsychotic-induced orthostatic hypotension.³ One study in rabbits showed midodrine's effectiveness in chlorpromazine-induced orthostatic hypotension.³ The case of a 60-year-old man with antipsychotic-induced orthostatic hypotension, recently managed on the inpatient psy-

chiatry service, illustrates the frustration providers and patients encounter with this occasionally treatment-resistant condition. A treatment algorithm for managing drug-induced orthostatic hypotension is presented.

The patient is a 60-year-old single, never married, Caucasian male with a history of schizophrenia dating back to his early twenties. The local community mental health team was managing his care, and he required a long-acting injectable because of his history of medication non-compliance. His regimen consisted of Haldol[®] Deconoate 200 mg injections every 4 weeks and Prozac[®] 10 mg daily. Despite his medication compliance, he experienced an exacerbation evidenced by increased preoccupation with bothersome, tormenting comments of his former landlord. His speech was rambling and disorganized. He exhibited blunted affect, social isolation, and decreased motivation. His hallucinatory experiences resulted in increased depressive symptoms with suicidal ideations and one attempt

of slitting his wrists. He had also begun to experience involuntary finger twitching and orobuccolingual dyskinesias. Because of his worsening psychosis, suicidal behavior, and need to adjust his medication regimen, he was admitted to the inpatient service.

INTERVENTIONS AND OUTCOMES

Given his recent relapse despite continued use of the medications, he was switched to oral risperidone with a goal of transition to an atypical long-acting injectable. His dosage was titrated up to 4 mg nightly. As his auditory hallucinations became less frequent and thoughts became more organized, he began to complain of intensifying dizziness and his blood pressure recordings were exceedingly low (i.e., 60s/30s). Given the likelihood fluoxetine was inhibiting the metabolism of the risperidone, thus, dramatically increasing his dosage, the risperidone and fluoxetine were both held. His orthostatic blood pressures were checked and noted to be grossly abnormal. Basic laboratory testing illustrated a mild anemia, which was present on admission. Thyroid studies and morning cortisol levels were within stated limits. ECGs and an echocardiogram were normal. Cardiac markers were not elevated. There was no other medical condition or neurological complaint that could account for his orthostatic hypotension.

Standard non-pharmacological treatment methods, including compression stockings, increased fluid and salt intake, and supine positional exercises, were utilized.⁴⁻⁷ Despite this, the patient required frequent intravenous fluid boluses to maintain his blood pressure and improve his dizziness. As his blood pressure stabilized, it was determined safe to reintroduce an antipsychotic.⁴⁻⁷ Paliperidone was substituted for risperidone in hope of transitioning to an atypical long-acting injectable that has less inclination for orthostatic hypotension. Fluoxetine was replaced by desvenlafaxine in hopes of utilizing the medication-induced increases in blood pressure. Despite the low dosage of paliperidone used, his orthostatic hypotension persisted. Therefore, it was felt at that point he would require adjuvant treatment with a first-line medication such as midodrine. Ten milligrams three times daily was initiated. Despite initial benefit, his orthostatic hypotension persisted and required addition of fludrocortisone 0.2 mg daily. The combination of these medications had little effect on his blood pressure and addition of 15 mg Adderall XR[®] was necessary. Interestingly, throughout his continued struggle with orthostatic hypotension and dizziness, his psychotic symptoms remained stable.

His dizziness and orthostatic hypotension did improve with the altered pharmacological regimen, and he was stabilized for discharge with hopes of slow titration off the supplementary medications.

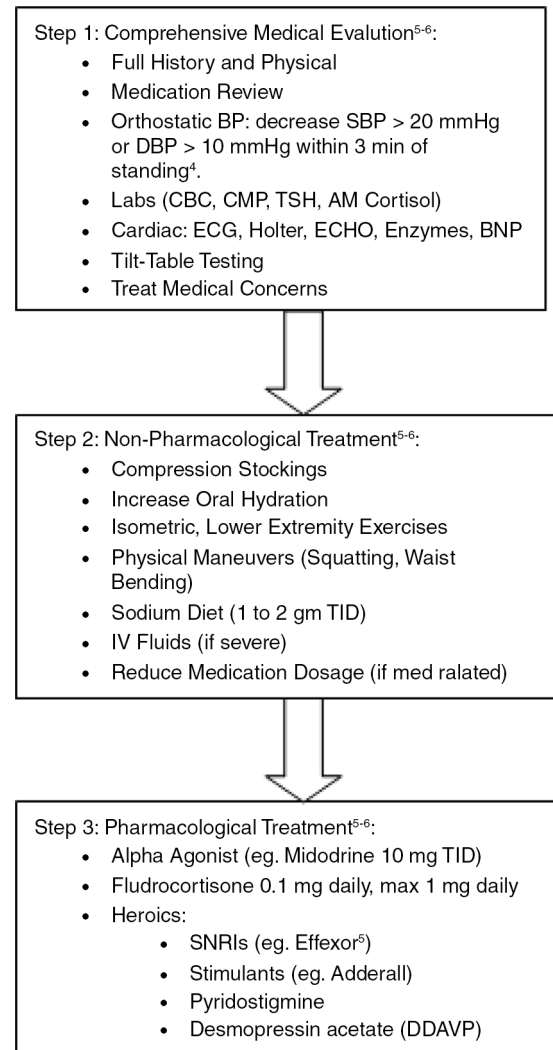


Figure 1. Proposed treatment plan for drug-induced hypotension with special consideration for antipsychotics. This protocol is an illustration of a step-by-step procedure if orthostatic hypotension remains refractory. The first step highlights the importance of confirming the diagnosis and ruling out other medical concerns. If orthostatic hypotension persists, the next step is use of non-pharmacological treatment. If the orthostatic hypotension remains, our protocol advises to rely on pharmacological treatment. Midodrine and fludrocortisone are commonly used first-line agents. Second- and third-line agents are also available if needed. From Refs. (2,5,6).

DISCUSSION

This case shows the frustration a highly resistant iatrogenic orthostatic hypotensive episode can create. Additionally, untreated orthostatic hypotension can lead to complications such as falls, myocardial infarction, stroke, and death. Both non-pharmacological and pharmacological methods were utilized and despite best efforts to manage the condition, eventual addition of three medications was necessary to prevent dramatic decreases in his blood pressures upon standing. Currently, there is no agreed upon management of antipsychotic-induced orthostatic hypotension and research in this area is limited. For example, Gugger proposed the use of midodrine and fludrocortisone for management, but also emphasized the lack of existing evidence.⁴ Therefore, these agents are used, but there is no consensus and strict protocol to follow. Figure 1 is a treatment regimen for drug-induced hypotension giving special attention to antipsychotic medications and the subject of this case report. This treatment development of a step-by-step protocol for refractory antipsychotic-induced hypotension. Furthermore, many studies propose the use of non-pharmacological treatment followed by midodrine and fludrocortisones as first-line treatments.^{3,4} However, similar to our case, these medications can prove futile and thus other agents, including desmopressin and pyridostigmine, are suggested in our protocol. Furthermore, our case and treatment protocol highlights the use of Adderall, which is an uncommon agent used to combat orthostatic hypotension and research into its effectiveness is limited. The proposed treatment regimen is the amalgamation of agents used in the literature but advocates for a unified standard protocol for all patients. In all, this case begs for alternative management of orthostatic hypotension created by antipsychotic medications to allow patients the opportunity to receive all the benefits these medications have to offer.

LEARNING POINTS

- Resistant anti-psychotic induced orthostatic hypotension is a common frustration shared among health-care professionals.
- Although non-pharmacological and pharmacological treatments are used commonly to eradicate this side effect, there is no consensus or standard protocol and there is limited research in this area.
- A standard treatment algorithm for managing drug-induced orthostatic hypotension is proposed in parallel with our case.
- Our protocol includes the amalgamation of current pharmacological treatments used but also highlights possible second-line and third-line agents.

Conflicts of interest and funding: The authors have not received any funding or benefits from industry or elsewhere to conduct this study.

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A Medical Student Initiated Elective Course in Business and Finance: A Needs Analysis and Pilot

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Background: As the knowledge needed by physicians expands past basic science and patient care, students are calling for their medical school education to do the same. At Michigan State University College of Human Medicine, students addressed this concern by developing a pilot elective, Medical Business and Finance (MBF). The goal of this student-led elective was to provide a basic understanding of personal finance, student debt handling, business management, and insurance reimbursement issues.

Methods: A preliminary needs assessment was conducted to discern if students wanted medical business and finance supplementation to the medical school curriculum. Ninety percent of students reported interest in a business and finance elective. Once the course was instated, student satisfaction and knowledge-base in medical business and finance was analyzed through pre-elective, pre-session and post-elective surveys.

Results: Results were analyzed on forty-eight students' pre-survey and post-survey responses. After the course, self-assessed student knowledge regarding finance and business nearly doubled. The average pre-elective self-assessed knowledge of finance was 3.02 on a ten-point scale and knowledge of business was 2.61. This was compared to an average post-elective self-assessed knowledge of 5.75 and 5.44, respectively. Satisfaction in MSU CHM business and finance resources also slightly increased at the completion of the course. Nearly 85% of students felt they benefited from participating in the elective. Similarly, 85% felt that incoming students would also benefit from taking the course. Almost 30% of students believed the material covered in the MBF Elective should be in the required medical school curriculum.

Conclusion: A student led elective can be an effective way to introduce students to an array of topics related to medical business and finance. Students felt that their knowledge of these topics increased and they valued the addition of medical business and finance education to their curriculum. A student-led elective is one potential way for others to successfully incorporate these topics into medical school curricula across the country.

Keywords: curriculum reform; medical business; medical finance; student-led; course; elective; module; student debt.

INTRODUCTION

In 2013, it was estimated that the United States spent \$2.9 trillion on health care, and it was projected that by 2022 health care alone will account for 20% of the gross domestic product.¹ In contemporary medicine, physicians are expected to know about the political, social, and economic context of medicine to decrease wasteful spending and practice appropriate parsimonious care. All of these foci require some understanding of the business of medicine.²

With increasing costs of medical education, there is a strong need for well-informed, knowledgeable medical students who can make educated financial decisions.³⁻⁷ Additionally, it has become known that student debt influences residency and other career decisions.⁸⁻¹² With the rapid change in the landscape

of health care, it is critical to prepare students to be literate in business and finance topics relevant to their field. Understanding how a cooperative practice works and how to minimize overhead costs, or even simply understanding what overhead costs are, allows students to step into practice more easily. It is essential for students to have financial and business literacy allowing them to join changing health care policy conversations dominated by the business and finance of medicine.

Prior Work and Current Need

Typically content in business and finance is not in the required medical school curriculum. However, some colleges offer certificate or dual degree programs

Table 1. Preliminary needs assessment survey

#	Question	Question type
1	How much knowledge do you feel you have in medical FINANCES?	Scaled (1–10)
2	How much knowledge do you feel you have in medical BUSINESS?	Scaled (1–10)
3	How fearful are you of the amount of debt you will incur in your medical education?	Scaled (1–10)
4	Do you feel you could benefit from this type of elective?	Multiple choice
5	Would you consider taking this elective?	Multiple choice
6	How important would provided food be in your decision to attend a weekly lunch elective?	Scaled (1–5)
7	If you are interested, what other speakers/topics would you like to see a part of the elective?	Free response

in medicine and business, and it is thought that graduates of these programs will become the future decision-makers and policy leaders in healthcare.^{13–16} Additionally, some residencies incorporate financial training in their programs to prepare graduates for practice with similar goals in mind.^{17–22}

At Michigan State University (MSU) College of Human Medicine (CHM), elective courses can be designed and administered by students. This process provides students an active role in their own education through course design. It also provides students the opportunity to address content that is important to them.

This report describes the development of a medical business and finance course and investigates the student satisfaction of the course using pre- and post-session surveys.

METHODS

Needs Analysis

Students of the MSU CHM class of 2016 completed a seven question needs analysis in the spring of 2013 exploring student interest in a business and finance elective shown in Table 1. The needs analysis was con-

ducted via the MSU CHM listserv of approximately 200 first-year medical students. Students were asked a series of questions that included ranking level of interest in an elective that would address topics in medical business and finance. Of the 106 respondents, 90% reported interest in a business and finance elective.

Syllabus, Content, and Course Delivery

Based on the strong need identified in the needs assessment, the student leaders developed the inaugural elective, 'Medical Business and Finance' (MBF) (Table 2). For the purposes of this course, 'medical business' was defined as the administrative cooperation of all persons involved in medical practice and 'medical finance' focused on the monetary aspects of medical education and the profession. The goal of the elective was to provide an introduction to business and finance topics including, but not limited to, insurance, reimbursement, contracts, investments, and loans.

First, the course syllabus was written to set scaffolding for course goals and requirements. Course topics were selected based on student feedback from the preliminary needs assessment (Table 3). Next, advisors were selected and IT support staff was enlisted to

Table 2. Tasks in planning the MBF Elective

Task	Curricular planning item
1	Writing the course syllabus
2	Selecting course faculty advisors and student coordinators
3	Reserving rooms on both preclinical campuses
4	Setting up video conferencing and IT
5	Developing course topics
6	Securing speakers for each session
7	Acquiring course approval by administration
8	Providing speaker gifts and parking reimbursement
9	Creating pre-elective, postsession and postelective surveys
10	Finding food sponsors
11	Applying for funding for course expenditures

Table 3. Session topics of the MBF Elective

Session	Topic
1	Introduction: Business and Finance in Medicine
2	Credit Reports and Taxes
3	Debt Forgiveness
4	Hospital Contracts
5	Investing, ROTH IRAs, and Stocks
6	Medical Billing and Coding
7	Physician's Panel
8	Intra-office Cooperation in Private Practice
9	Life, Disability and Malpractice Insurances
10	Advocacy Training for Physicians and Patients
11	Final Discussion and Summary

manage simultaneous broadcasts between two MSU CHM campus sites, East Lansing and Grand Rapids, MI.

Course speakers were secured through faculty, student-leader connections, and support from local medical societies. Their expertise ranged from private business owners to practicing physicians (MSU and non-MSU faculty) to financial counselors. Care was taken to secure speakers who were experts in their field. Some were either practicing physicians with direct experience in medical business and finance while others had medical provider clients with whom they worked closely in the medical business and finance sectors.

Once a tentative schedule was established, the course was approved by the MSU CHM administration as a one-credit university elective (HM590). The MSU Institutional Review Board evaluated the study of this elective and deemed it exempt. In the fall of 2013, the MBF Elective was offered, and 63 first- and second-year medical students (including the three student leaders) were enrolled.

Curriculum Overview

The elective was scheduled once weekly over the lunch hour 12:00–12:50 PM for 10 consecutive weeks. There was also one evening panel of physicians for a total of 11 sessions. The lunch hour time slot allowed students to attend sessions after morning lectures while still remaining on time for afternoon labs or other activities. The presentations were delivered live at one campus and simultaneously broadcasted to the other. An attempt was made to distribute live speakers evenly between both the Grand Rapids and East Lansing campuses. These sessions began promptly at noon in order to assure full engagement with the guest speakers. Lunch was sponsored by our local Ingham County Medical Society and Kent County Medical Society during these sessions.

Class Description

Guest speakers were free to design their assigned 50-min session guided by pre-session questions provided by the students. Teaching and learning strategies ranged from informal question and answer sessions to prepared PowerPoint presentations and case presentations. Speakers typically brought support handouts to provide to students. Additionally, speakers were instructed not to promote their company or products to students. After the presenter finished, students asked questions and presenters were given thank you cards and small gift bags.

Course Evaluation

Students' self-assessed knowledge was measured via a SurveyMonkey® questionnaire before the first session of the elective (45 questions) and after the last session (32 questions). The survey administered during the first session was the same survey administered after the last session with some questions added or subtracted based on relevance to the course timeline. The survey consisted of questions regarding student demographic information, self-assessed medical business and finance knowledge, expected physician business and finance knowledge, and suggestions for course improvement.

After each session, students rated the quality of the presenter and content with a 10-question survey and provided questions for the next speaker. Questions were sent to the speaker in advance of their presentation to focus discussion around student interest and areas of inexperience.

Course Requirements

Students were required to take both pre- and post-elective surveys, attend and complete 80% of the elective sessions and postsession surveys, and be present at the final 'wrap-up' class. Students meeting these criteria earned one course credit hour. The three student leaders did not participate in course surveys.

RESULTS

Sixty-three students were originally enrolled in the course, including three student leaders. Six students did not give consent for their survey data to be released; six students withdrew from the course. Including the three student leaders, 15 students in total were excluded from analysis. Results were analyzed on 48 students' presurvey and postsurvey responses.

Figure 1 depicts what level of business and finance knowledge students thought practicing physicians ought to know as reported in the postelective survey.

Figure 2 compares students' pre- and postelective responses about medical business and finance. After the course, self-assessed student knowledge regarding finance and business nearly doubled. The average pre-elective self-assessed knowledge of finance was 3.02 on a 10-point scale and knowledge of business was 2.61. This was compared to an average postelective self-assessed knowledge of 5.75 and 5.44, respectively. Satisfaction in MSU CHM business and finance resources also slightly increased at the completion of the course, as did students' self-reported fear of debt from their medical education. The amount of knowledge

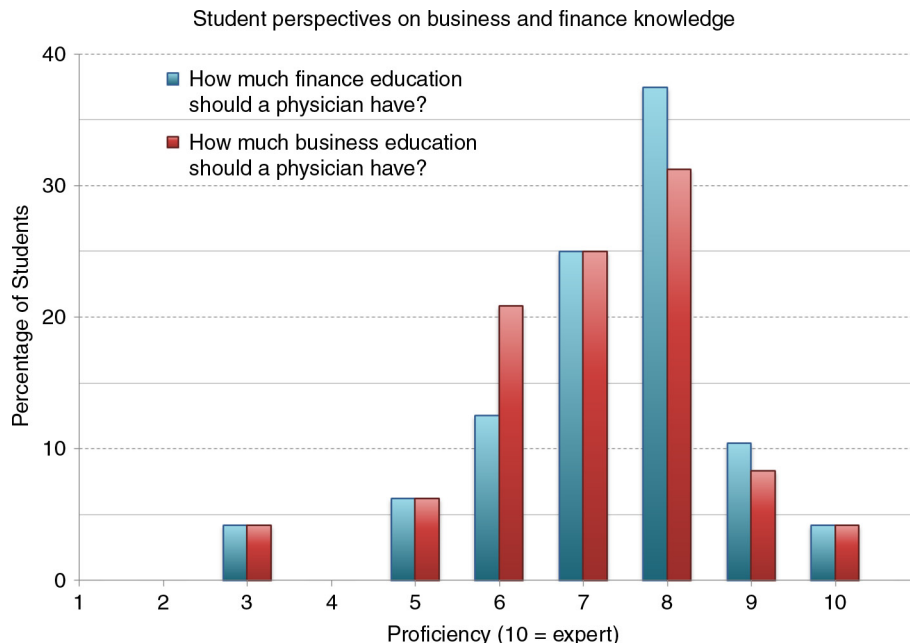


Figure 1. Students’ perspective on how much business (red) and finance (blue) knowledge practicing physicians’ should have (with 1 = ‘novice’ and 10 = ‘expert’). Data obtained from postelective survey. *N* = 48.

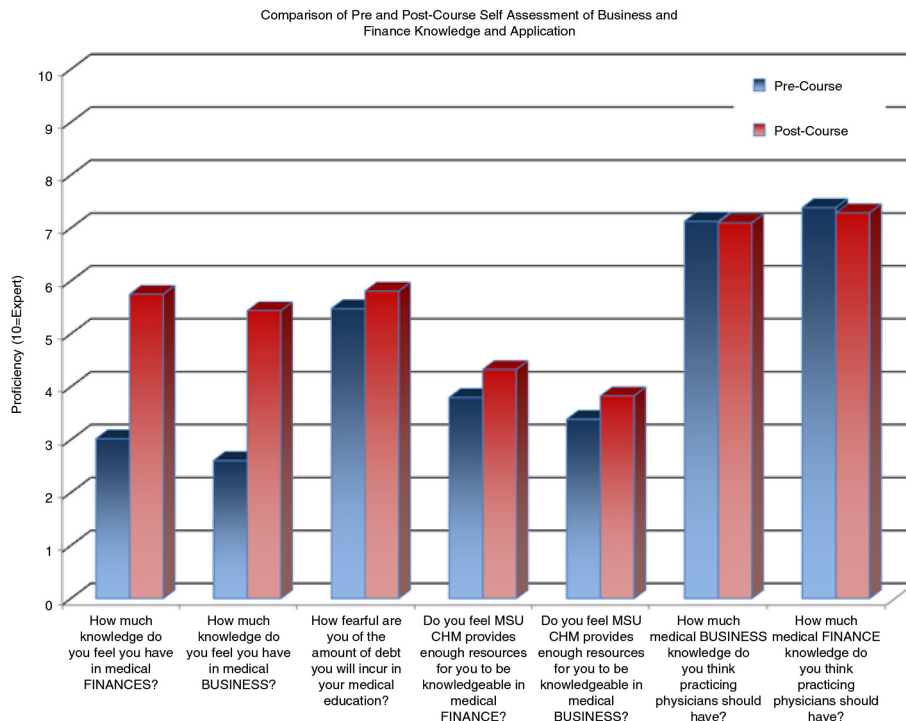


Figure 2. Students’ responses to pre- and postelective surveys (with 1 = ‘novice’ or ‘completely disagree’ and 10 = ‘expert’ or ‘completely agree’). Data obtained from pre-elective survey (red) and postelective survey (blue). *N* = 48.

students felt practicing physicians should have regarding business and finance was nearly identical before and after participating in the course.

Student Satisfaction

Students were asked about the perceived value of the MBF Elective. Nearly 85% of students felt they benefited from participating in the elective. Similarly, 85% felt that incoming students would also benefit from taking the course. Almost 30% of students believed the material covered in the MBF Elective should be in the required medical school curriculum.

DISCUSSION

Medical students are generally aware of the debt required to become a physician, but appreciating the impact of debt typically evolves over time.⁸⁻¹² As students progress through medical school, many realize they have questions and concerns about business and finance that the curriculum may not address. It has been documented that students worry about their debt load and that fear of debt, in some part, influences specialty decisions.^{11,12} Although not a significant increase, the results of the postelective survey suggest that students who took the elective became more concerned about the debt they were accumulating after the elective was completed.

The timing of the surveys may cause some bias in the survey results. It is possible that the fear of debt accumulation may again decrease over time after the students are no longer having weekly discussions about finance. To address this bias, it would be appropriate to resurvey the students at a later time to determine the longevity of their fear of debt accumulation.

Additionally, results demonstrate that the knowledge students seek can be provided effectively through a student-led initiative. After exposure to the 10-week MBF Elective, students' perceived knowledge almost doubled in both medical business and finance according to pre- and postelective surveys, as shown in Fig. 2.

There was a considerable gap between students' pre-elective self-assessed knowledge of finance (3.02/10) and expected physicians' knowledge (7.34/10). The gap also existed in business knowledge, 2.61/10 and 7.12/10, respectively. After the elective, students' knowledge base doubled in both business and finance, making their expectation of the level of knowledge they need to obtain as a physician a more attainable goal.

Recommendations

Although a student-led elective may be effective, this structure can also be difficult to maintain. One of the challenges of student-run electives is that the course leaders come and go, making sustainability difficult. Consistent faculty advisors may alleviate some of this problem and add some stability to the process. The student leaders of this pilot elective have found new leadership from rising second-year students and faculty leaders have stayed the same. The MBF Elective is currently being offered for its second year. Using the results from the postsession survey, the new leaders were able to discern which topics were favorable or unfavorable to students and alter the course schedule accordingly. For example, 'Hospital Contracts' and 'Investing, ROTH IRAs, and Stocks' were deemed the most useful topics and 'Intra-office Cooperation in Private Practice' and 'Final Discussion and Summary' were considered the least useful. Furthermore, presession survey results guided the new leaders to keep the same speakers or identify new ones for a favored topic.

As always, beginning course planning and preparation early every year is vital to have the elective run smoothly. The new leadership was selected well in advance of this year's iteration to allow ample time to begin working. Additionally, it is important to recognize that curriculum development will be influenced by the new student leaders' and faculty's community connections. These connections serve as the foundation for securing speakers and are a confounding variable in the topic selection. This may also produce variability in course preparation in other institutions.

Summary Statement

A student-led elective can be an effective way to introduce students to an array of topics related to medical business and finance. Students felt that their knowledge of these topics increased and they valued the addition of medical business and finance education to their curriculum. A student-led elective is one potential way for others to successfully incorporate these topics into medical school curricula across the country.

Conflict of interest and funding: Michigan State University College of Human Medicine provided funding for this course. None of the authors have any proprietary interests or conflicts of interest related to this submission.

Disclaimer: Kent County Medical Society and Ingham County Medical Society provided lunches for the elective sessions.

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Alzheimer's Disease: A Clinical and Basic Science Review

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Alzheimer's disease (AD) is the most common cause of dementia in older adults and an important public health problem. The purpose of this review article is to provide a brief introduction to AD and the related concept of mild cognitive impairment (MCI). The article emphasizes clinical and neurobiological aspects of AD and MCI that medical students should be familiar with. In addition, the article describes advances in the use of biomarkers for diagnosis of AD and highlights ongoing efforts to develop novel therapies.

Keywords: Alzheimer's disease; mild cognitive impairment; dementia; neurodegeneration; neuroimaging; biomarkers.

INTRODUCTION

The world's population is rapidly aging, and the number of people with dementia is expected to grow from 35 million today to 65 million by the year 2030. In the United States alone, 5 million or 1 in 9 people over the age 65 are living with Alzheimer's disease (AD), the most common cause of dementia. For comparison, according to the Centers for Disease Control and Prevention (2009–2012 estimates), about 3 million older adults in the United States have asthma, 10 million have diabetes, 20 million have arthritis, and 25 million have hypertension. Primary care physicians and specialists alike will encounter older adults with dementia at an increasing frequency during their careers. As dementia carries significant implications for patients, their families, and our society, it is imperative for well-rounded physicians to have a solid understanding of this topic. The purpose of this review article is to provide a brief introduction to AD and the related concept of mild cognitive impairment (MCI). The article emphasizes clinical and neurobiological aspects of AD and MCI with which medical students should be familiar. In addition, the article describes advances in the use of biomarkers for diagnosis of AD and highlights ongoing efforts to develop novel therapies.

ALZHEIMER'S DISEASE

Alois Alzheimer and Auguste D

The German psychiatrist and neuropathologist Dr. Alois Alzheimer is credited with describing for the first time a dementing condition which later became known as AD. In his landmark 1906 conference lecture and a subsequent 1907 article, Alzheimer described the case of Auguste D, a 51-year-old woman with a 'peculiar disease

of the cerebral cortex,' who had presented with progressive memory and language impairment, disorientation, behavioral symptoms (hallucinations, delusions, paranoia), and psychosocial impairment.^{1–3} Remarkably, many of the clinical observations and pathological findings that Alzheimer described more than a century ago continue to remain central to our understanding of AD today.

Dementia

Dementia is a clinical syndrome (a group of co-occurring signs and symptoms) that involves progressive deterioration of intellectual function.⁴ Various cognitive abilities can be impaired with dementia, including memory, language, reasoning, decision making, visuospatial function, attention, and orientation. In individuals with dementia, cognitive impairments are often accompanied by changes in personality, emotional regulation, and social behaviors. Importantly, the cognitive and behavioral changes that occur with dementia interfere with work, social activities, and relationships and impair a person's ability to perform routine daily activities (e.g., driving, shopping, housekeeping, cooking, managing finances, and personal care). Table 1 summarizes the clinical criteria for all causes of dementia.^{4,5}

There are several reversible and irreversible causes of dementia.^{4,6} Reversible dementias (also referred to as 'pseudo-dementias') are relatively rare but potentially treatable and occur secondary to another medical condition, including depression, nutritional deficiencies (e.g., vitamin B12), metabolic and endocrine disorders (e.g., hypothyroidism), space occupying lesions (e.g., brain tumor), normal pressure hydrocephalus, or substance

Table 1. Clinical criteria for dementia

-
1. Progressive impairment in two or more areas of cognition:
 - a) Memory (ability to learn and remember new information)
 - b) Language (speaking, reading, writing)
 - c) Executive function (reasoning, decision making, planning)
 - d) Visuospatial function (ability to recognize faces and objects)
 - e) Praxis (ability to perform purposeful movements)
 - f) Changes in personality, mood, or behavior
 2. Cognitive deficits:
 - a) Interfere with functioning (ability to perform activities of daily living)
 - b) Represent a decline from previous levels of functioning
 - c) Are not due to delirium or psychiatric disorder (e.g., depression)
 - d) Are established using history from patient, corroborated by informant (e.g., family member), and objective cognitive assessment
-

Adapted from Ref. [5].

abuse. Certain classes of medications also have the potential to cause cognitive impairment in older adults (e.g., anti-cholinergics, psychotropics, analgesics, sedative-hypnotics). Irreversible (primary) dementias involve neurodegenerative and/or vascular processes in the brain. AD is the most common cause of irreversible dementia, accounting for up to 70% of all dementia cases in the United States.⁷ Other types of primary dementia include vascular dementia (10–20%), dementia associated with Parkinson's disease, dementia with Lewy bodies, and frontotemporal dementia.

Epidemiology of AD

AD is a critical public health issue in the United States and many other countries around the world, with a significant health, social, and financial burden on society. An estimated 5 million Americans have AD, with a new diagnosis being made every 68 sec.⁸ In the United States, AD is the fifth leading cause of death among older adults, and about \$200 billion are spent annually on direct care of individuals living with dementia. Worldwide, it is estimated that 35 million people have AD or other types of dementia, and about 65 million people are expected to have dementia by 2030 (115 million by 2050).⁹

AD is a multifactorial disease, with no single cause known, and several modifiable and non-modifiable risk factors are associated with its development and progression. Age is the greatest risk factor for the development of AD. The likelihood of developing AD increases exponentially with age, approximately doubling

every 5 years after age 65.^{10,11} The vast majority of individuals suffering from AD are aged 65 or older and have 'late-onset' or 'sporadic' AD (>95% of all cases). Rare genetic mutations are associated with the development of AD before age 65, which is known as 'early-onset' or 'familial' AD (<5% of all cases).¹² People with familial forms of AD have an autosomal dominant mutation in either one of the presenilin genes located on chromosomes 1 and 14 or in the amyloid precursor protein (APP) gene located on chromosome 21. In addition, individuals with Down's syndrome (trisomy 21) have an increased risk of developing early-onset AD. The genetics of sporadic AD are more complex and less well understood. It is known that the epsilon four allele of the apolipoprotein E (APOE) gene located on chromosome 19 is a risk factor for the development of sporadic AD.¹³ The prevalence of AD is higher among females, reflecting the longer life expectancy of women.¹⁴ Lower educational attainment has been associated with increased risk of AD dementia,¹⁰ consistent with the idea that education serves to increase a person's cognitive reserve and resilience to AD pathology.¹⁵ A large body of evidence suggests that cerebrovascular risk factors play a significant role in both the development and progression of AD; people with a history of diabetes, hypertension, obesity, and smoking have a substantially elevated risk of AD.¹⁶ Family history of AD in first-degree relatives and a history of head injury with loss of consciousness are also risk factors for the development of AD.⁴

Neuropathology of AD

AD is a progressive neurodegenerative brain disorder that causes a significant disruption of normal brain structure and function. At the cellular level, AD is characterized by a progressive loss of cortical neurons, especially pyramidal cells, that mediate higher cognitive functions.^{17,18} Substantial evidence also suggests that AD causes synaptic dysfunction early in the disease process, disrupting communication within neural circuits important for memory and other cognitive functions.¹⁹ AD-related degeneration begins in the medial temporal lobe, specifically in the entorhinal cortex and hippocampus.²⁰ Damage to these brain structures results in memory and learning deficits that are classically observed with early clinical manifestations of AD. The degeneration then spreads throughout the temporal association cortex and to parietal areas. As the disease progresses, degeneration can be seen in the frontal cortex and eventually throughout most of the remaining neocortex. Of note is the fact that AD causes pronounced

damage to multiple components of the limbic system,^{12,21} including the hippocampal formation and the major fiber tracts that connect it to the cerebral cortex (fornix and cingulum), amygdala, cingulate gyrus, and thalamus. This widespread pattern of neurodegeneration, affecting both limbic and neocortical regions, correlates closely with the array of cognitive deficits and behavioral changes that AD patients exhibit.¹² In addition to cognitive impairment across multiple domains (memory, language, reasoning, executive, and visuospatial function), patients with AD show an impaired ability to perform activities of daily living and often experience psychiatric, emotional, and personality disturbances.

It has been theorized that the neuronal damage seen in AD is related to the deposition of abnormal proteins both within and outside of neurons. These are the hallmark pathological lesions of AD known as 'plaques and tangles.' The abnormal proteins are deposited in the cerebral cortex following a stereotypical pattern of spread along neural pathways that mediate memory and other cognitive functions.¹⁸ 'Senile plaques' are extracellular accumulations of amyloid protein and consist of insoluble amyloid-beta protein (A β). Normally, cells throughout life release soluble A β after cleavage of the APP – a cell surface receptor. AD involves abnormal cleavage of APP that results in the precipitation of A β into dense beta sheets and formation of senile plaques. It is believed that microglia and astrocytes then mount an inflammatory response to clear the amyloid aggregates, and this inflammation likely causes destruction of adjacent neurons and their neurites (axons and dendrites).^{11,18} 'Neurofibrillary tangles' (NFT) are intracellular aggregates of abnormally hyper-phosphorylated protein tau, which in normal form serves as a microtubule stabilizing protein and plays a role in intracellular (axonal and vesicular) transport. It is possible that NFT interfere with normal axonal transport of components necessary for proper neuronal function and survival (e.g., synaptic vesicles with neurotransmitters, neurotrophic factors, and mitochondria), eventually causing neurons to die.^{11,18} Substantial evidence supports the idea that amyloid formation and deposition in the cerebral cortex is one of the earliest pathological processes in AD, preceding the clinical onset of the disease by 10–20 years.¹² Despite this, the temporal sequence of events in the deposition of amyloid plaques and formation of NFT during development of AD remains open to debate. In fact, a recent study suggests that the initial formation of NFT may occur in the brainstem rather than the medial

temporal lobe and may precede the appearance of the first amyloid plaques in the neocortex.²²

Diagnosis of AD

The gold standard for the diagnosis of AD is an autopsy-based (post-mortem) pathological evaluation. The presence and distribution of amyloid plaques and NFT in the brain is used to establish the diagnosis of 'definitive' AD and stage the disease.²² In clinical settings, the diagnosis of AD is largely based on medical history, physical and neurological examinations, and neuropsychological evaluation, as well as the exclusion of other etiologies using selective ancillary testing. The clinical diagnosis of AD has an accuracy of 70–90% relative to the pathological diagnosis, with greater accuracies being achieved in specialty settings such as memory disorder clinics.²³ The cornerstone of the clinical diagnosis is a set of consensus criteria first established in 1984²⁴ and last updated in 2011 by the National Institute on Aging – Alzheimer's Association (NIA-AA) workgroup.⁵ The NIA-AA clinical criteria for the diagnosis of 'probable' AD dementia are summarized in Table 2. When the patient's cognitive impairment has an atypical clinical course or is suspected to be due to other etiologies in addition to AD, the diagnosis of 'possible' AD dementia is recommended. Patients with AD generally have normal findings on physical and neurological examinations.^{6,25} To help with the differential diagnosis, Table 3 summarizes some of the clinical features that distinguish

AD dementia from other causes of irreversible dementia.

Laboratory and neuroimaging studies are used only for investigational purposes or as an adjunct to the clinical criteria for AD, particularly to rule out structural brain lesions and identify 'reversible' causes of dementia. The only laboratory studies that the American Academy of Neurology recommends to be performed on a routine basis as part of dementia work-up are serum B12, thyroid stimulating hormone (TSH), and free thyroxine

Table 2. Clinical criteria for probable AD dementia

1. Presence of dementia (as per criteria in Table 1)
2. Gradual onset of symptoms over months to years
3. History of progressive cognitive decline
4. Initial presentation may be amnesic (typical) or non-amnesic (atypical)
5. No evidence for another cause of cognitive impairment: cerebrovascular disease, other dementia syndromes, or neurological/medical disease

Adapted from Ref. [5].

Table 3. Clinical features that distinguish AD from other dementias

Clinical feature	Alzheimer's dementia	Vascular dementia	Parkinson's dementia	Dementia with Lewy bodies	Frontotemporal dementia
Patient profile	> 65 years old	> 40 years old Vascular risk factors	> 65 years old	75 years old (mean)	50–70 years old 50% autosomal dominant
History	Gradual onset and deterioration	Acute onset, step-wise deterioration	Gradual onset and deterioration	Gradual onset and deterioration	Gradual onset and deterioration
Initial symptoms	Memory loss	Executive dysfunction	Visual hallucinations	Visual hallucinations Fluctuating attention	Memory intact Disinhibition, apathy or aphasia
Physical findings	No motor impairment (until late stage)	Pyramidal (upper motor neuron) signs	Parkinsonism (precedes dementia by > 1 year)	Parkinsonism (presents within 1 year of dementia)	Usually none (rarely associated with motor neuron disease)

Notes: Pyramidal (upper motor neuron) signs include hyperreflexia, spasticity, weakness, and extensor plantar responses (Babinski sign). Parkinsonism refers to the following features: bradykinesia, cogwheel rigidity, resting tremor, and postural instability. Information compiled from Refs. [4, 25].

(T4) levels.²⁶ Structural magnetic resonance imaging (MRI) or non-contrast computed tomography (CT) may be useful to rule out normal pressure hydrocephalus, cerebral hematomas, brain tumors, and cerebrovascular lesions.

Treatment of AD

There is no cure for AD, and drug therapy for the disease is still in its infancy. Approved medications for the treatment of probable AD help control the symptoms of AD but do not slow down the progression or reverse the course of the disease itself.¹² At present, the mainstay of AD therapy are drugs that target neurotransmitter systems in the brain. AD primarily damages glutamate- and acetylcholine-producing neurons and their associated synapses, and this damage correlates well with early cognitive symptoms of AD.¹⁹ Acetylcholinesterase inhibitors help improve memory function and attention in AD patients by interfering with the breakdown of acetylcholine, thereby increasing the levels of the neurotransmitter at the synapse. There are currently three FDA-approved cholinesterase inhibitors:²⁷ *rivastigmine* and *galantamine* (for mild to moderate AD), and *donepezil* (for all stages of AD). *Memantine* is another FDA-approved medication for use in moderate to severe AD but belongs to a different class of drugs known as NMDA (glutamate) receptor antagonists.²⁷ Both classes of medications are generally well-tolerated, with gastrointestinal upset, dizziness, and headache being the most common adverse effects observed.

In recent years, a number of potential disease-modifying AD drugs have been evaluated in clinical trials, and several others are being evaluated in ongoing trials.

Drugs that act to decrease the amount of A β protein in the brain have received the most attention due to the prominent pathogenic role ascribed to A β in the AD literature. One class of such drugs are secretase inhibitors, which inhibit the secretase (protease) enzymes that cleave APP to produce A β .^{28,29} Another strategy that has been attempted is by using drugs that promote the clearance of A β through active or passive immunization.³⁰ Unfortunately, as of the writing of this article, several completed phase three trials with different amyloid-lowering drugs have failed to demonstrate clinical efficacy.³¹ Various explanations have been proposed to account for the repeated clinical trial failures observed with these disease-modifying agents. One possibility is that A β may play a less prominent or different role in AD pathogenesis than previously hypothesized,^{32,33} an issue certain to remain controversial in the near future. Regardless, other therapeutic strategies for AD are being investigated alongside the amyloid-based therapies, although with no major clinical successes yet to report. A promising avenue is the development of drugs that target the abnormal tau protein comprising the NFT.³¹ Another important source for potential AD drugs is the pool of medications on the market that are already approved for non-AD indications, such as diabetes, hypertension, and infectious disease. This strategy of drug 'repurposing' or 'repositioning' can greatly expedite the discovery of novel AD treatments and has been used in the past for other neurodegenerative disorders (e.g., anti-viral drug amantadine for use in Parkinson's disease).³⁴ An alternative explanation for the clinical trial failures is that the trials were conducted in patients with mild to moderate AD

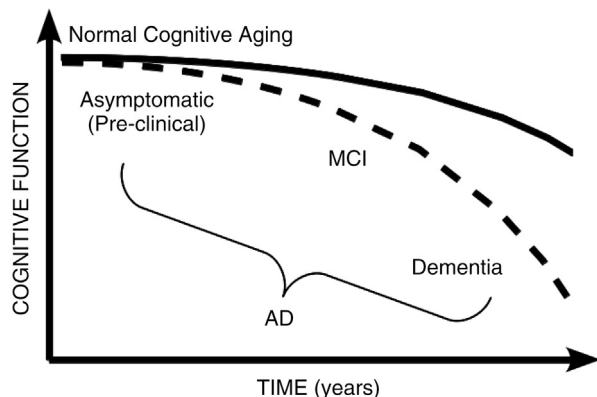


Figure 1. Progressive development of Alzheimer's disease (AD). The relationship among pre-clinical, mild cognitive impairment (MCI), and dementia stages of AD (dashed line) is shown relative to normal cognitive aging (solid line). Adapted with permission from Elsevier.³⁷

dementia, at a stage when the disease process is likely irreversible and brain damage is too great for the anti-AD therapy to have a clinically significant effect. Early diagnosis of AD and timely therapeutic intervention is critical given that the disease may begin years or even decades prior to the onset of dementia.^{12,35} As such, greater emphasis is being placed on conducting clinical trials in populations of persons with no dementia who are at risk for developing AD, such as individuals with MCI.³⁶

MILD COGNITIVE IMPAIRMENT

The MCI Concept

MCI is a syndrome characterized by memory and/or other cognitive impairments that exceed the decline in cognition associated with the normal aging process. MCI is often regarded as a precursor to dementia or a transitional state between healthy cognitive aging and dementia (Fig. 1).³⁷ The most widely used clinical criteria for the diagnosis of MCI are those proposed by Petersen and colleagues at the Mayo Clinic (Table 4).³⁸ Researchers have also proposed several subtypes of MCI based on distinct neuropsychological profiles.³⁹ Amnesic MCI involves memory-only impairments, while non-amnesic MCI involves only impairments in cognitive domains other than memory (e.g., executive function/attention, language, and visuospatial function). Multi-domain MCI is characterized by impairments in both memory and non-memory functions.

Epidemiology of MCI

Large population-based epidemiological studies³⁹⁻⁴¹ in both the US and Europe have estimated that the

Table 4. Clinical criteria for MCI

1. Subjective cognitive complaint, preferably corroborated by an informant
2. Objective memory and/or other cognitive impairments that:
 - a) Are abnormal for the individual's age and education, as documented using neuropsychological testing
 - b) Represent a decline from previous levels of functioning
3. Normal ability to perform activities of daily living
4. Absence of dementia

Adapted from Ref. [38].

prevalence of MCI among adults aged 65 and older is 3–24%, with higher prevalence in older individuals. Prospective longitudinal studies indicate that patients with MCI exhibit annual rates of progression to dementia of 3–15%, with highest rates for people in specialty clinic-based cohorts as compared to those in community-based cohorts.^{42,43} Overall, rates of progression from MCI to dementia are elevated well above the annual 1–2% incidence rate of dementia in the general older adult population.³⁹ Among MCI patients who convert to dementia, AD is the most prevalent etiology.⁴⁰ However, progression risks vary according to MCI subtype; amnesic MCI and multi-domain MCI subtypes progress more frequently to AD whereas non-amnesic MCI progresses more frequently to non-AD forms of dementia, including vascular dementia.^{39,41} Furthermore, patients with multi-domain MCI have a greater risk of developing AD than those with single-domain amnesic MCI.⁴⁴ While many individuals with MCI develop dementia, a substantial proportion remain cognitively stable or even improve, reverting to normal cognitive status (Fig. 2).⁴¹ Taken as a whole, epidemiological research suggests that MCI is a useful concept that describes the pre-dementia stage of AD but that it is a heterogeneous clinical syndrome in terms of both etiology and outcomes.^{39,45,46}

BIOMARKERS OF AD AND MCI

Several neuroimaging and other biomarker approaches are being used to study AD and MCI. In the short term, biomarkers of AD are needed to improve the selection of patients in clinical trials, while in the long term biomarkers are needed to identify high-risk patients for early treatment as well as for monitoring disease progression and response to treatment. This section describes some of the widely used biomarker approaches and the related findings in AD and MCI.

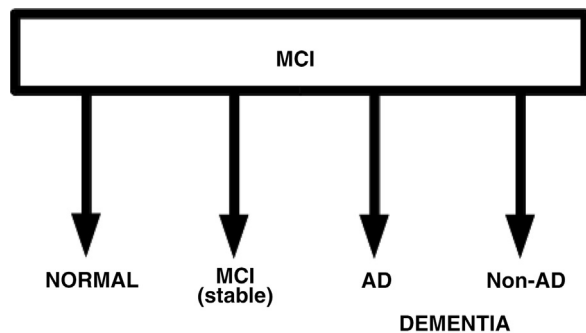


Figure 2. Clinical outcomes in patients with mild cognitive impairment (MCI). Many patients with MCI eventually develop dementia, either due to Alzheimer's disease (AD) or other causes (e.g., cerebrovascular). However, a substantial proportion of MCI patients stay cognitively stable and some even revert to normal cognitive status.

Magnetic Resonance Imaging

MRI uses a strong magnetic field and radio frequency waves to non-invasively characterize the structure of the brain by measuring the energy released by protons within various tissue components, such as gray matter, white matter, and cerebrospinal fluid (CSF). Volumetric MRI has been used to study regional patterns of brain atrophy in patients with MCI and AD.^{20,47,48} Medial temporal lobe atrophy, involving the hippocampus and entorhinal cortex in particular, is the earliest and most prominent MRI feature evident in AD and predicts progression from MCI to AD dementia.⁴⁹ On volumetric MRI, AD patients also show marked enlargement of the lateral ventricles, portions of which are adjacent to the medial temporal lobe.⁵⁰ Diffusion tensor imaging (DTI) is another MRI-based technique that, by measuring the diffusion of water molecules, is able to delineate the organization of white matter in the brain and allows researchers to quantitatively assess the integrity of white matter fiber tracts.⁵¹ DTI studies have shown that AD and MCI disrupt major white matter pathways in the brain, especially those within the limbic system (e.g., fornix and cingulum).^{21,52} Finally, functional MRI (fMRI) is a neuroimaging technique that indirectly assesses brain function by measuring blood-oxygen-level-dependent (hemodynamic) activity. One promising application of fMRI (known as 'resting-state' fMRI) is the measurement of intrinsic brain activity, which occurs irrespective of any external stimulation.⁵³ Resting-state fMRI studies have shown that AD and MCI are associated with decreased communication (functional connectivity) within the default mode network (DMN), a network of brain

regions involved in memory and internal information processing.⁵²

Positron Emission Tomography

Positron emission tomography utilizing 18F-fluorodeoxyglucose (FDG-PET) as a radioactive tracer is a nuclear imaging technique which measures regional brain metabolism. The earliest sign of AD detectable on an FDG-PET scan is the hypometabolism of the posterior cingulate cortex and precuneus.⁵⁴ This hypometabolism is also detectable at the MCI stage of the disease.⁵⁵ FDG-PET has also proven to be of value in distinguishing different forms of dementia, especially AD versus frontotemporal dementia.^{55,56} A recent advance is the development of *in vivo* PET-based amyloid imaging, which uses a special radioactive ligand that binds to amyloid plaques in the brain. Pittsburgh compound B (PiB) is a carbon-11-based amyloid-labeling ligand that is widely used in the research setting. Patients with AD show increased binding of PiB in temporal, parietal, and frontal brain regions, indicating widespread cortical distribution of amyloid deposition.⁵⁷ The FDA approved a different amyloid-labeling ligand, the fluorine-18-based florbetapir, for clinical use in 2012.⁵⁸ PET-based amyloid imaging is a novel and exciting diagnostic tool that non-invasively detects one of the hallmark molecular lesions of AD, but there remain several practical concerns about its use in the clinical setting. In addition to its high cost, there is a concern about the clinical utility of a positive amyloid scan. While a negative amyloid scan appears to rule out that a patient's cognitive impairment is due to AD (high negative predictive value), a positive amyloid scan is much less informative because it can be positive in many cognitively normal older adults and people with other non-AD neurological conditions (low positive predictive value).⁵⁹ For now, PET-based amyloid imaging is not covered by Medicaid or Medicare for routine clinical use in AD patients but only approved for limited use (e.g., to rule out AD or for selection of patients in clinical trials).⁶⁰

Fluid Biomarkers

CSF-based and blood plasma-based protein biomarkers are also being investigated for diagnosis of AD. Several studies have used immunoassays to measure the levels of various proteins in the CSF, finding that patients with AD show decreased levels of the 42 amino acid isoform of the A β (A β -42) peptide and elevated levels of the phosphorylated tau (P-tau) peptide.^{61,62} A recent longitudinal study showed that baseline A β -42/P-tau ratio could accurately predict the progression

from MCI to AD.⁶³ In 2007, plasma biomarkers were proposed as a promising alternative to CSF biomarkers for early detection of AD.⁶⁴ In recent years, other studies have examined the clinical utility of cell-signaling, immune, metabolic, and disease-related plasma proteins, but findings have been inconsistent.^{65–67} Overall, furtherwork must be done to standardize the measurement of CSF and plasma proteins and to determine the clinical utility of protein biomarkers for diagnosis of AD.

CONCLUSION

Since Alois Alzheimer described the first case of AD more than a century ago, much progress has been made in understanding the biology and clinical aspects of the disease. Substantial advances have been made in characterizing pre-dementia stages of AD, such as MCI, and improving the diagnostic and therapeutic options available for managing AD. Our ability to find the 'cure' for AD ultimately depends not only on having an accurate view of the cellular and molecular processes that go awry but also on having optimal biomarkers to enable early diagnosis and timely therapeutic intervention in at-risk individuals. Recognizing the urgent need to develop clinically useful neuroimaging and other biomarkers for the early detection of AD, the NIA sponsored the ongoing Alzheimer's Disease Neuroimaging Initiative (ADNI) beginning in 2004.⁶² The ADNI, which is akin to the Framingham Heart Study in its ambitions, is a public-private partnership and the largest project of its kind that seeks to collect longitudinal neuroimaging data along with clinical data, neuropsychological assessments, and biological specimens (e.g., blood and CSF) from MCI, AD, and healthy older subjects. The ADNI and similar large-scale initiatives are likely to rapidly advance our knowledge on dementia and AD and will catalyze the development of significantly more effective therapies for AD than exist today. To conclude, the reader is left with some important issues that must be resolved in the future as we move toward a 'cure' for AD in the 21st century:

- (1) What is the optimal combination of biomarkers for (a) early detection of AD; and (b) monitoring disease progression and response to treatment?
- (2) What is the optimal therapeutic strategy for (a) prevention of AD; (b) treatment of AD; and (c) sporadic versus familial AD? (i.e., therapeutic targets, role of medications versus lifestyle modification, optimal time to intervene)

- (3) What are the potential benefits and harms associated with shifting the therapeutic strategy from (a) one that involves treating people with overt AD dementia to (b) one where we treat people with MCI, and ultimately to (c) one where we treat people who are asymptomatic but show an AD-like biochemical and/or imaging biomarker pattern? Are we moving closer to treating abnormal lab results as opposed to the patient? For example, would we be abiding by the oath to 'first, do no harm' by treating an asymptomatic person who shows an AD-like biomarker pattern but is not destined to develop cognitive impairment (e.g., due to his/her high cognitive reserve or resilience in the face of AD pathology).

Acknowledgements: I would like to thank Andrea Bozoki, MD (Michigan State University, Department of Neurology), for reviewing the material in this article on diagnosis and treatment. I am grateful to my grandmother Khana for inspiring me to conduct research on Alzheimer's disease and to pursue a career in clinical neuroscience.

Conflicts of interest and funding: The author declares no conflicts of interest. This work was funded by the DO/PhD Program, The Graduate School, and the Department of Neurology at Michigan State University.

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Comparing Current Screening Modalities for Colorectal Cancer and Precancerous Lesions: Is Colonoscopy the Method of Choice?

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Colorectal cancer (CRC) is the third most common form of cancer and the second leading cause of cancer death in the Western world. Presently, screening tools such as colonoscopy, sigmoidoscopy, fecal occult blood test (FOBT) and computed tomographic colonography (CTC) are available for CRC screening. The debate over which screening tool is most effective in detecting CRC and precancerous lesions is ongoing. Many recent studies have identified colonoscopy as the most sensitive and specific screening modality for CRC. However, a number of factors have prevented colonoscopy from being widely accepted. Less invasive techniques such as sigmoidoscopy and CTC are growing in popularity among physicians and patients who are apprehensive about colonoscopy screening; although many still are yet to experience the procedure first-hand. This literature review will attempt to validate the growing theory that colonoscopy is superior to other modalities for the diagnosis and screening of CRC and reduces the risk of CRC mortality. In order to do so, the paper will compare the risks and benefits of colonoscopy to sigmoidoscopy and CTC. It will further look at the different aspects that encompass a patient's decision to partake in screening, such as basic knowledge about CRC, history of CRC in the family, advice from physicians and individual beliefs about what screening entails. Finally, this paper will propose ways in which colonoscopy screening can be improved and thus surpass other screening modalities to universally become the first choice for CRC screening.

Keywords: colonoscopy; colorectal neoplasms; sigmoidoscopy; CT colonography; mass screening.

INTRODUCTION

Colorectal cancer (CRC) is the third most common form of cancer and the second leading cause of cancer death in the Western world, equally affecting both men and women.¹ In 2012, the United States had an estimated 143,460 individuals diagnosed with CRC and 51,690 related deaths.² The vast majority of CRCs within North America are sporadic with fewer than 5% directly related to chronic inflammatory diseases or hereditary causes of CRC, such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colon cancer (HNPCC).¹ Sporadic CRC is due to mutations causing histological changes within the luminal aspect of colonic mucosa which slowly progress to benign adenomatous polyps of varying types: tubular, tubulovillous and villous.³ These precancerous lesions can increase in size, become dysplastic and eventually transform into overt carcinomas. The slow progression of these changes causes age to be one of the greatest risk factors for CRC. It is estimated that 90% of all CRC cases occur after the age of 50 in both men and women.⁴ Along with family history and age, other significant risk factors for CRC include obesity, tobacco

and alcohol abuse, stress, inflammatory bowel diseases (e.g., ulcerative colitis) and diet.³ With its long list of risk factors and worldwide prominence, it is imperative that health care providers and patients become more knowledgeable about CRC and the ways in which to detect its precursor lesions at early and docile stages.

A number of different techniques are currently employed to screen for polyps and CRC. Epidemiological studies have shown a decline in the incidence and mortality of CRC over the years, which is primarily attributed to increases in screening test use.⁵ Specific guidelines outlining which tests should be used and when they should be administered have been established by a number of prominent medical societies and organizations. The United States Preventative Services Task Force (USPSTF) recommends three main screening methods: high-sensitivity fecal occult blood test (FOBT) annually, flexible sigmoidoscopy every 5 years with FOBT every 3 years or colonoscopy every 10 years.⁵ The American Cancer Society and The American College of Physicians' (ACP) recommendations mirror those of USPSTF. These bodies also agree that patients with one

or more first-degree relatives with CRC, or a hereditary syndrome that predisposes them to CRC, should receive screening in the second or third decade of life,⁶ while in average-risk patients, screening should be done between the ages of 50 and 75.⁷ There is a strong belief that screening after the age of 75 may no longer be beneficial for patients and may in fact cause harm.^{4,6}

Since the 1990s, the dominant screening test for CRC in the United States has been colonoscopy.⁸ Colonoscopy allows for direct visualization of the entire colon, from the appendiceal orifice to the dentate line, and also facilitates biopsy sampling or polypectomy of lesions that may appear abnormal. However, there is still an ongoing debate in the medical community over which screening test is superior in the prevention and detection of CRC. Moreover, with the introduction of newer screening methods such as Computed Tomographic Colonography (CTC) and fecal DNA testing, choosing the best screening method has become more difficult for both physicians and patients.

This paper will review both the advantages and disadvantages of colonoscopy, sigmoidoscopy and CTC. The paper will forgo discussion of FOBT as it attempts to focus on invasive screening techniques that are more procedurally similar to colonoscopy so that aspects of the patient experience during each technique can be appropriately compared. Other factors affecting a patient's decision to engage in regular CRC screening and the role of primary care providers in informing their patients about each method will also be analyzed.

Through a contemporary literature review, this paper will examine whether colonoscopy is the superior method for the diagnosis and screening of CRC, and thus whether it has a greater capacity to reduce the risk of death from CRC as compared to other screening modalities.

METHODS

The main database used to obtain scholarly articles cited in this literature review was PubMed at www.pubmed.org. A number of different search strategies were used to narrow down articles. One strategy included keywords such as: ((colon cancer) AND (colonoscopy) AND (surveillance)). Another strategy used 'colonoscopy', 'epidemiology' and 'colorectal neoplasms' as MeSH terms with 'mass screening OR screening.' Subsequent searches focused on other modalities of CRC screening with the use of 'sigmoidoscopy' and 'CT colonography' as MeSH terms and with the sub-heading 'therapeutic use.' The filters used in all searches

included: past 5 years (2008–2013), clinical trial, randomized control trials (RCTs), humans, English and full text available. A few articles were also attained from other databases such as Medscape, EBSCOhost and Google Scholar using variations of the search strategies, keywords and filters described above.

In all articles selected, the study population of interest was high- and low-risk patients, aged 50 or older, living within North America and other developed nations. Other inclusion criteria included choosing articles that were published in prominent journals or by recognized and valued medical organizations.

Criteria used to exclude articles from this paper include factors such as a small study population and articles categorized as 'review articles', although a limited number were consulted to obtain relevant background information on the pathophysiology, epidemiology and diagnosis of CRC.

Articles that met these criteria were then compiled into an 'Evidence Table' (Table 1) that outlines the key findings of each.

RESULTS

Comparing Colonoscopy to Sigmoidoscopy and CTC

Colonoscopy

Colonoscopy is a screening method that allows inspection of the entire colon and enables biopsy of neoplastic lesions through polypectomy. This method is conducted under sedation and is currently the leading tool for CRC screening.⁸ Many of the presently known benefits of colonoscopy stem from population-based cohort studies that analyze the effects of colonoscopy on incidence and mortality among communities around the world. In Ontario, Canada, Rabeneck et al⁹ conducted a large prospective study between 1993 and 2006 where they found the rates of complete colonoscopy screening increased in all regions of the province. Within the population that underwent screening, the incidence rates and mortality rates of CRC were lower in the younger age group (50–69 years) and lower for women within all age groups. When mortality rate was adjusted for confounding factors associated with increased risk of CRC death, such as increased age, male gender, lower income and rural residence, greater colonoscopy use was overall associated with decreased mortality from CRC. Furthermore, the study identified that for every 1% increase in colonoscopy rates in the cohort's individual region of residence (each participant was assigned to 1 of 13 regions based on their address in Ontario), there

Table 1. Evidence table outlining articles analyzed in this review

First author	Date of publication	Study design	Level of evidence	Study population	Therapy or exposure	Outcome/results
Adler, Andreas	2013	Prospective cohort without controls	4	21 colonoscopists were studied from private practices in Berlin, between Oct. 2006 and Mar, 2008. Overall, a total of 12,134 colonoscopies were examined.	Colonoscopy	Three patient factors correlated with adenoma detection rate (ADR): age, sex and low quality of bowel preparation. Factors that accounted for 41.4% of inter-physician variability in ADR included: the number of CME meetings attended and differences in equipment used during screening.
Atkin, Wendy	2013	RCT	1	1,580 patients, 55 years or older (median age was 68 years; range 61–75), with symptoms suggestive of CRC (change in bowel habits, rectal bleeding or abdominal pain) from 21 UK hospitals. 1,047 were randomly assigned to colonoscopy and 533 assigned to CTC. 864 (55%) of the cohort were women. Patients were recruited between Mar. 2004 and Dec. 2007.	CTC and colonoscopy	160 (30%) patients in the CTC group had additional colonic investigation compared with 86 (8.2%) in the colonoscopy group. Almost half the referrals after CTC were for small (<10 mm) polyps or clinical uncertainty. Detection rates of CRC or large polyps were 11% for both procedures. CTC missed 1 of 29 CRC and colonoscopy missed none (of 55)
Baxter, Nancy N.	2009	Case control	3	10,292 case patients and 51,460 controls were part of this study population. Five controls matched by age, sex, geographic location and socioeconomic status were randomly selected for each case patient. Participants were between the ages of 52 and 90 who received a CRC diagnosis from Jan. 1996 to Dec. 2001 and died of CRC by Dec. 2003.	Colonoscopy	Complete colonoscopy was strongly associated with fewer deaths from left-sided CRC but not from right-sided CRC
Baxter, Nancy N.	2012	Case control	3	A total of 9,458 cases were identified. Patients were aged 70–89 and diagnosed with CRC between Jan. 1998 and Dec. 2002. Three controls (patients without CRC) were matched to each case. The primary exposure in the cases was colonoscopy performed from 1 Jan. 1991 to 6 months before the reference date. All case and control data were collected from the SEER-Medicare data.	Colonoscopy	Colonoscopy is associated with a reduced risk of death from CRC, with a stronger detection rate for distal vs. proximal CRC. The overall association of reduced risk of death was strongest if colonoscopy was performed by a gastroenterologist, as opposed to surgeons or primary care providers.

Table 1 (Continued)

First author	Date of publication	Study design	Level of evidence	Study population	Therapy or exposure	Outcome/results
Bretagne, Jean-Francois	2010	Retrospective cohort	3	<p>Eighteen endoscopists were used in this study; 14 worked in private practice and 4 worked in public hospitals.</p> <p>The screening group included asymptomatic men and women aged between 50 and 74 with no other risk factor for CRC.</p> <p>The study was conducted between 2003 and 2007 in Ille-et-Vilaine, Brittany.</p> <p>The first round of screening was in 2003 and 2004 with 213,635 participants and the second round in 2005 and 2006 with 224,504 participants.</p>	Colonoscopy	<p>Interendoscopic variability had no effect on cancer detection in a screening program with a high compliance rate with colonoscopy after FOBT; however, it did influence the identification of adenomas.</p>
Courtney, Ryan J.	2013	Case series without controls	4	<p>1,592 at-risk individuals (56–88 years of age) were randomly selected from the Hunter Community Study (a longitudinal community cohort in Australia) between Dec. 2004 and Dec. 2007 to take part in a questionnaire by mail.</p> <p>1,117 participants returned the questionnaires; 760 respondents were eligible for screening and analysis.</p>	Colonoscopy	<p>63% of participants received CRC screening, with the majority being 'potentially high risk' participants (84%). Those significantly more likely to have received testing were aged between 65 and 74 and who had at some point received screening advice from their family physician, or had discussed family history of CRC with their doctor.</p> <p>21% of those in the 'at or slightly above average-risk' group had received screening as per official screening guidelines.</p> <p>Guidelines were significantly more likely to be followed in the 'moderately increased risk or potentially high risk' groups (45%).</p> <p>Colonoscopy within 5 years was the most commonly recommended guideline and was significantly more likely to be recommended to individuals with private insurance or who had discussed family history of CRC with a doctor.</p>
de Wijkerslooth, Thomas R.	2012	RCT	1	<p>This study was of 8,844 Dutch citizens aged 50–74, invited by mail for population-based CRC screening in Amsterdam and Rotterdam, between Jun. 2009 and Aug. 2010. Invitations were randomly allocated 2:1 to colonoscopy (5,924) or CTC (2,920)</p>	Colonoscopy and CTC	<p>Before screening, individuals expected colonoscopy and bowel preparation to be more burdensome than CTC screening. However, when individuals participated in screening, CTC was scored as more burdensome than colonoscopy.</p>

Table 1 (Continued)

First author	Date of publication	Study design	Level of evidence	Study population	Therapy or exposure	Outcome/results
de Wijkerslooth, Thomas R.	2012	RCT	1	Allocation was stratified for age, sex, SES status based on data of Statistics Netherlands Between Jun. 2009 and Aug. 2010, 8,844 individuals aged 50–75, never before screened for CRC, were randomly allocated to undergo either colonoscopy screening (5,924) or CTC (2,920). Allocation was based on age, sex and socioeconomic status; data from Statistics Netherlands. Patients were from the Amsterdam and Rotterdam region.	Colonoscopy and CTC	The most frequently cited reasons to accept screening were early detection of precursor lesions and CRC, and contribution to science. The most frequently cited reasons to decline were the unpleasantness of the examination, the inconvenience of the preparation, a lack of symptoms and 'no time/too much effort'. Elderly individuals cited the absence of symptoms as a more significant reason to not undergo colonoscopies as compared to the overall study population. The most frequently cited reason for declining colonoscopy was the unpleasantness of the examination. As compared to patient visits without CRC screening discussion, visits with discussion were associated with increased perceived and screening intention after the visit but no significant change in perceived benefits, barriers or self-efficacy. Within 6 months, 17 of 38 patients (45%) who discussed screening completed screening compared with 0 of 12 patients who did not discuss screening.
Fenton, Joshua J.	2011	Prospective cohort	3	The study population included patients attending appointments at 2 academic primary care clinics – University of California, Davis, and Medical Center in Sacramento, CA, between Sept. 2008 and Dec. 2009. 50 patients aged between 50 and 75 were eligible for CRC based on the criteria that they had never had: FOBT during the past year, flexible sigmoidoscopy during the past 5 years, colonoscopy in 10 years. In addition, 20 family care physicians were selected from the 2 clinics.	Colonoscopy	Sensitivities of OC, CTC, FS, FIT and FOBT for advanced colonic neoplasia were 100,96.7, 83.3, 32 and 20%, respectively. Combination of FS with FIT or FOBT did not increase sensitivity for advanced CRC.
Graser, A.	2009	Prospective cohort without controls	4	311 asymptomatic, average-risk adults (171 men and 140 women), aged between 50 and 81 underwent same day screening of 5 different screening interventions. Only 307 patients completed it in full, as 4 subjects withdrew.	Sigmoidoscopy CTC, FIT, FOBT, Colonoscopy	

Table 1 (Continued)

First author	Date of publication	Study design	Level of evidence	Study population	Therapy or exposure	Outcome/results
Hoff, Geir	2009	RCT	1	<p>Exclusions criteria included the absence of specific symptoms of colonic disease (melena, hematochezia, diarrhea, relevant changes in stool frequency or abdominal pain). Subjects were also excluded if they had prior OC within the last 5 years, positive family history for CRC, a history of or present IBD, hereditary CRC syndromes, a body weight greater than 150 kg or severe cardiovascular or pulmonary disease.</p> <p>The study included 13,653 subjects in the screening group (of which only 8,846 attended screening), and 41,092 subjects were in the control group.</p> <p>Groups consisted of an equal number of men and women, aged 55–64, who were randomly selected from 2 areas in Norway: city of Oslo and Telemark county (urban and mixed urban and rural populations).</p> <p>The study was conducted from Jan. 1999 to Dec. 2000.</p>	Sigmoidoscopy	<p>Reduction in incidence of CRC with flexible sigmoidoscopy screening was not seen after 7-year follow-up.</p> <p>Mortality from CRC was not significantly reduced in the screening group.</p>
Johnson, C. Daniel	2008	Case series without controls	4	<p>The study included 2,531 asymptomatic patients, 50 years or older who underwent CTC followed by same day colonoscopy between Feb. 2005 and Dec. 2006.</p> <p>Patients were excluded if they presented any symptoms of CRC (anemia, melena, hematochezia) more than once in the past 6 months, if they had IBD, hereditary colorectal disease, if they had received colonoscopy in the past 5 years or had a positive FOBT result.</p>	CTC and colonoscopy	<p>CTC identified 90% of the adenomas or cancers measuring 10 mm or more in subjects.</p>
Ko, Cynthia W.		Retrospective cross-sectional study	4	<p>A total of 328,167 colonoscopies were conducted by 12,910 providers (either gastroenterologists, surgeons (general or colorectal) or primary care physician</p>	Colonoscopy	<p>Gastroenterologists were most likely and general surgeons were least likely to detect polyps during colonoscopy.</p> <p>Diagnostic biopsy rates were highest for family physicians and lowest for colorectal surgeons.</p>

Table 1 (Continued)

First author	Date of publication	Study design	Level of evidence	Study population	Therapy or exposure	Outcome/results
Leiberman, David A.	2000	Case control	3	Asymptomatic adults were selected from 13 Veterans Affairs medical centers in the United States, between Feb. 1994 and Jan. 1997. 17,732 patients were screened for enrolment; 3,196 were enrolled; 3,121 of the enrolled patients (97.7%) underwent complete colonic examination. The mean age of the patients was 62.9 years, and 96.8% were men.	Colonoscopy	Snare polypectomy and polyp removal rates were highest for gastroenterologists and lowest for family physicians. Colonoscopy can detect advanced colonic neoplasms in asymptomatic adults which cannot be detected with sigmoidoscopy.
Manser, Christine N.	February 2012	Non-randomized prospective cohort	2	1912 screened and 20,774 control participants from a rural area of Switzerland	Colonoscopy	Colonoscopy with polypectomy significantly reduced CRC incidence and cancer-related mortality in the general population.
Rabeneck, Linda	2010	Population-based prospective cohort	3	This study included 2,412,077 participants aged between 50 and 90 (mean age of 64) in Ontario, Canada. Of the cohort, 84.2% lived in an urban area, 53.7% were women and 86.5% had a co-morbidity score of 0. Each member of the cohort was assigned to 1 of 13 regions based on their address in the province. Patients were excluded if they had a previous diagnosis of CRC, ulcerative colitis, Crohn's disease or had their residence in the South East Local Health Integration Network during the time of the study.	Colonoscopy	Increased colonoscopy use was associated with mortality reduction from CRC at the population level.
Singh, Harminder	2010	Population-based prospective cohort	3	32,306 individuals from Manitoba, Ontario, who had negative results on initial colonoscopy screening between Apr. 1, 1987 and Sept. 30, 2007. Study population included patients aged between 50 and 80. Individuals outside this age range, those with prior sigmoidoscopy, IBD, resective colorectal surgery or CRC were excluded.	Colonoscopy	There was a 29% reduction in overall CRC mortality and a 47% reduction in mortality from distal CRC (SMR), but no reduction in mortality from proximal CRC The reduction in mortality from distal CRC remained significant for greater than 10 years

Table 1 (Continued)

First author	Date of publication	Study design	Level of evidence	Study population	Therapy or exposure	Outcome/results
Schoen, Robert E.	2012	RCT	1	A total of 154,900 men and women aged 55–74 participated in this study from 1993 through 2001. Individuals were randomly assigned to either an intervention group (screening with flexible sigmoidoscopy with repeat screening at 3–5 years) or to the usual care group.	Sigmoidoscopy	Incidence of CRC after a median follow-up of 11.9 years was 11.9 cases per 10,000 person-years in the intervention group, as compared with 15.2 cases per 10,000 person-years in the usual-care group. Reductions were seen in incidence of CRC in both proximal and distal colon. Mortality was reduced by 50% only in distal CRC with no change in proximal. In the short-term analysis, patients are more likely to accept CTC as a better method of surveillance than colonoscopies. However, after long-term follow-up, patients noted that colonoscopy offered some benefits
von Wagner, Christian	2012	RCT	1	547 patients with symptoms suggestive of CRC who were randomly assigned at a ratio of 2:1 to undergo either colonoscopy (362) or CTC (185). Of these, 388 responded to a post-test questionnaire; 212 women (55–87 years old) and 176 men (55–96 years old). 337 patients responded to the follow-up questionnaire; 199 women (55–87 years old) and 138 men (55–92 years old).	Colonoscopy and CTC	
Zalis, Michael E.	2012	Prospective cohort without controls	4	605 asymptomatic men and women, aged 50–85, with moderate to average risk of CRC were recruited from four institutions: Massachusetts General Hospital; Brigham and Women's Hospital; University of California, San Francisco Veterans Affairs Medical Center; and North Shore Medical Center, between Jun. 2005 and Oct. 2010	Non-cathartic CTC and colonoscopy	Non-cathartic CTC was able to accurately detect adenomas 10 mm or greater but less accurate for smaller lesions when compared to colonoscopy screening of same cohort

RCT = randomized control trials; CTC = computed tomographic colonoscopy; OC = optical colonoscopy; FS = flexible sigmoidoscopy; FIT = fecal immunochemical stool testing; FOBT = fecal occult blood testing; CRC = colorectal cancer; IBD = inflammatory bowel disease.

was a statistically significant decrease in the hazard of death by 3%.⁹

Similar results showing significantly decreased CRC incidence and mortality in groups undergoing colonoscopy screening were found in two other population-based prospective studies conducted by Manser et al¹⁰, in Switzerland, and by Singh et al¹¹ in Manitoba, Canada. Singh et al¹¹ analyzed a cohort of individuals who had previously undergone CRC screening with only colonoscopy between April 1984 and September 2007 and had received negative results (no polyps/CRC). The overall reduction in CRC mortality within the screened population of this study was 29%, with the largest reduction in mortality rates (39%) seen during a 5–10 year follow-up, as compared to the general population.¹¹ Importantly, the study also found there were differences in the mortality rates associated with specific locations in the colon. There was a statistically significant 47% reduction in distal CRC deaths, but no reduction in deaths from proximal CRC.¹¹ The reduction in mortality due to distal CRC remained significant for up to 10 years following the study's conclusion.¹¹ A case-control study carried out by Baxter et al¹² presented mirroring results, finding that colonoscopy screening not only decreased CRC mortality in cases vs. controls but also that this screening was associated with fewer deaths from left-sided CRC as compared to right-sided.¹²

Many recent studies have discovered that discrepancies during colonoscopy-specific detection of CRC and precancerous lesions may be operator dependent. Bretagne et al¹³ identified that differences in the performance of 18 endoscopists analyzed in their study resulted in large ranges of adenoma detection rates (ADR). However, when assessing the detection rate of actual CRC, these operator-dependent factors did not independently influence the varied range of rates, as patient age and sex also played a role.¹³ Another study by Adler et al¹⁴ went on to identify what it believed were the specific factors that defined the efficacy and quality of screening by colonoscopists. The most statistically significant associations, with 41.4% of the inter-physician variability in ADR, were the number of Continuing Medical Education (CME) meetings each colonoscopist attended and the characteristics of their individual instruments.¹⁴

Some researchers investigated if the specific specialties of those carrying out colonoscopies played any role in the variability of ADR and CRC detection. Baxter et al¹⁵ found that although colonoscopy screening reduced the risk of CRC mortality (regardless of the

specialty of the endoscopist), there was a stronger association if a gastroenterologist performed the colonoscopy as opposed to a non-gastroenterologist (e.g., a surgeon or primary care provider). Conclusively, gastroenterologists provided significantly more protection from CRC death than other providers.¹⁵ A study by Ko et al¹⁶ further identified variability in frequency of procedures performed by each specific specialty (Fig. 1). Overall, multivariate analysis determined that non-gastroenterologists were least likely to detect and remove polyps, and likelihood of diagnostic biopsy was significantly lower for all surgeons (general/colorectal).¹⁶

Sigmoidoscopy

Unlike colonoscopy, flexible sigmoidoscopy is performed without sedation, has limited bowel preparation and is thus more often provided by general practitioners or non-physicians.¹ The use of flexible sigmoidoscopy CRC screening was analyzed in a German observational study by Graser et al¹⁷ and two RCTs: the PLCO trial conducted by Schoen et al¹⁸ and the first of the three Norwegian Colorectal Cancer Prevention (NORCCAP) trials carried out by Hoff et al.¹⁹

The PLCO trial mirrored findings presented in many older observational trials that showed flexible sigmoidoscopy conferring protection against CRC mortality and incidence.⁸ In this study, a 21% reduction in CRC incidence was observed in the intervention group as compared to the usual care group, and CRC incidence in specific locations of the colon also showed significant reductions: 29% in the distal colon and 19% in the proximal.¹⁸ Overall, CRC mortality was reduced by 26% in the intervention group as compared to the usual-care group. However, when observing location-specific mortality rates in distal and proximal parts of the colon, the PLCO trial found that distal CRC mortality was reduced by 50%, but no significant change in mortality was observed for proximal CRC (143 and 147 deaths; relative risk, 0.97; 95% CI, 0.77–1.22; $P = 0.81$).¹⁸

Compared to the PLCO trial, the NORCCAP trial observed a larger reduction in mortality rates (59%) among subjects who took part in sigmoidoscopy screening.¹⁹ Nevertheless, like the PLCO trial, some findings of NORCCAP also substantiated discrepancies in cancer mortality rates among discrete locations of the colon when sigmoidoscopy was performed. Among the intervention group, a greater reduction in both incidence and mortality (76%) of rectosigmoidal cancer was found as opposed to CRC.¹⁹ Thus, benefits of sigmoidoscopy

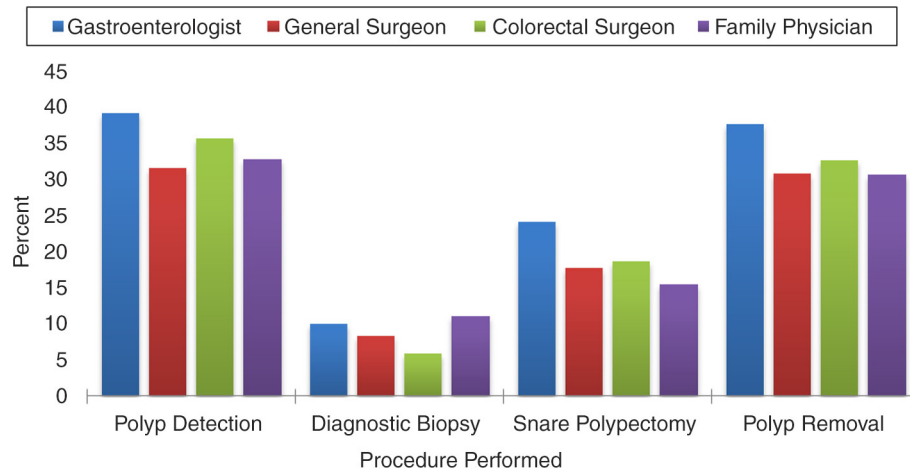


Figure 1. Variability in rate of polyp detection, biopsy and polyp removal among provider specialty. Gastroenterologists have the highest rate of polyp detection, polypectomy and polyp removal. General surgeons are least likely to detect polyps, while colorectal surgeons have the lowest diagnostic biopsy rate. Family physicians have the highest rate of biopsy, but lowest rate of polyp removal. (Modified from Ko et al.¹⁶)

were once again shown to be limited to areas of the distal colon.

The last study analyzing sigmoidoscopy screening was a prospective study carried out by Graser et al.¹⁷ The sensitivities of five different screening methods: sigmoidoscopy, CTC, colonoscopy, fecal immunochemical stool testing (FIT) and FOBT were all tested in parallel among asymptomatic subjects. Flexible sigmoidoscopy was 83.3% sensitive for advanced colonic neoplasia (CRC) and only 68% sensitive to adenomas ≥ 10 mm. Combining sigmoidoscopy with FOBT or FIT enabled an increased detection of large adenomas (76.2 and 71.4%, respectively) as compared to sigmoidoscopy alone (68%). However, when these tests were combined for the detection of advanced CRC, no increase in sensitivity was observed. Although flexible sigmoidoscopy showed to be a superior test to FOBT and FIT, it was unable to surpass the advanced sensitivity of colonoscopy and CTC in detection of CRC and adenomas of all sizes.¹⁷

Computed Tomographic Colonography

CTC is a minimally invasive screening tool that is currently undergoing testing in a number of trials. Like colonoscopy, CTC provides examination of the entire colon and rectum; however, it allows for computerized 3D and advanced 2D imaging not available with colonoscopy.¹ In order to compare the efficiency of CTC to colonoscopy in CRC screening and detection, three observational studies and one UK-based multicenter RCT were analyzed.^{17,20,21}

All three observational studies focused on comparing the sensitivity and specificity of CTC in detecting adenomas of various sizes and neoplastic lesions to that of colonoscopy, with additional comparison to other screening modalities (sigmoidoscopy, FIT and FOBT) completed by Graser et al.¹⁷ The study populations assessed in all three studies were comparable and included average risk, asymptomatic patients (each study using similar exclusion criteria) who were aged 50 or older.^{17,20,21} All studies presented similar results (Table 2).

Although similarities between the sensitivity and specificity of CTC and colonoscopy for the detection of large neoplastic lesions were found, discrepancies became evident in all studies when detecting adenomas of smaller sizes, specifically between 5 and 6 mm in diameter (Table 2). All three studies concluded that CTC was significantly less sensitive for smaller lesions than colonoscopy. Measurements of specificity showed similar trends.^{17,20,21} In two of the studies, the median sizes of missed lesions were 7 mm²¹ and 6 mm.²⁰ Graser et al¹⁷ found that CTC only missed one adenoma with advanced histology in the <10 mm size group.

The UK-based RCT carried out by Atkin et al²² presented similar findings to those seen in the observational studies. The sensitivity of CTC to CRC was 85% in this RCT as compared to 93% with colonoscopy. Still, the most significant discrepancy in CTC screening presented by this study was its discovery that a greater number of patients assigned to the CTC screening

Table 2. Differences in sensitivity and specificity of CTC and colonoscopy in detecting adenomatous lesions of various sizes

Study	CTC (large lesions; > 10 mm)		CTC vs. Colonoscopy (small lesions; 5–6 mm)	
	Sensitivity (%)	Specificity	Sensitivity (%)	
Graser et al ¹⁷	96.7	n/a	59.2	94.6
Johnson et al ²⁰	90	86%	78	100
Zalis et al ²⁰	91	85%	59	76

Colonoscopy and CTC have similar efficacy in detecting large lesions; however, colonoscopy is significantly more sensitive than CTC for smaller lesions.

group needed to undergo additional colonic investigations (after initial screening) as compared to the colonoscopy group (30.0% vs. 8.2%).²² Within the colonoscopy group, the major reason for additional screening was incomplete colonoscopy (did not reach the cecum) as seen in 11.3% of patients. In contrast, the major causes for additional CTC investigations were low predictive value for CRC or polyps ≥ 10 mm (15.6%) and failure to confirm the presence of small (< 10 mm) polyps (9.2%). In both cases, the additional investigation was a new or repeat colonoscopy; a more invasive procedure than CTC. Finally, this RCT was the only study to identify a statistically significant difference in men and women with regard to the need for additional investigations after screening. Men were six times more likely to need further investigation after CTC compared to colonoscopy, while women were only two times more likely.²²

Patient Experience, Education and Compliance

Patient experiences, perspectives on CRC screening and compliance to screening guidelines were also analyzed. Research conducted by von Wagner et al²³ found that individuals undergoing colonoscopy were significantly less satisfied, more worried, experienced more physical discomfort and reported more adverse effects such as 'feeling faint or dizzy' than those taking part in CTC screening. This study further noted that patients had a better experience with CTC screening than with colonoscopy.^{17,20–22} However, this initial dissatisfaction with colonoscopy was not absolute, as von Wagner et al²³ identified that patients undergoing CTC had a greater number of post-procedure referral rates as compared to those who took part in colonoscopy screening (33% vs. 7%). Thus, the study concluded that after 3 months, patients reported greater satisfaction with the long-term outcomes of their colonoscopy screening compared to CTC²³; a result also found by Atkin et al.²²

It is likely that because the overall benefits of colonoscopy are not known by patients initially, the negative connotations surrounding CRC screening are factors that deter patients from actually fulfilling screening guidelines. A RCT conducted by de Wijkerslooth et al²⁴ examined the reasons for participation and non-participation in CRC screening among a study population who had never undergone screening in two regions of the Netherlands. This study found that the most significant reason to participate in CRC screening (either colonoscopy or CTC) was 'it allows early detection of precursor lesions' (the most decisive reason in both screening modalities; 72% for colonoscopy vs. 68% for CTC).²⁴ The most significant reason for non-participation with respect to colonoscopy was 'the examination strikes me as unpleasant' (66%) while for CTC the reasons were both lack of time and absence of symptoms.²⁴ A second RCT looked at the 'expected' burden of screening before colonoscopy or CTC and compared it to the actual ('perceived') burden experienced during either procedure.²⁵ This research discovered that although participants expected colonoscopy to be more burdensome than CTC, in reality they experienced significantly more overall burden with CTC (79% with colonoscopy vs. 82% with CTC).²⁵

Many of the reasons mentioned for and against screening participation stem from a lack of patient knowledge about CRC and its prevention, and most importantly from a lack of doctor–patient communication about specific guidelines for screening. A case series by Courtney et al²⁶ identified that within their study population, only 63% of the cohort had ever received any sort of CRC screening (FOBT/ sigmoidoscopy or colonoscopy), with the majority of this subset being 'potentially high risk' participants (84%). Overall, individuals significantly more likely to have received testing were those who were either between the ages of 65 and 74, had at some point received screening

advice from their family physician or had discussed family history of CRC with their doctor.²⁶

Similar results permeated from a prospective study by Fenton et al²⁷ which took a deeper look at what a group of physicians actually discussed with patients during visits. In 76% of the interactions, physicians discussed CRC screening for a median time of 2.5 min. Physicians described one or two modalities for screening, with colonoscopy always being mentioned. Doctors discussed benefits of CRC screening in more than half of the encounters, but less often commented on risks/susceptibility to CRC, barriers to screening, or self-efficacy of screening. After all visits were complete, it was found that patients in the discussion group had a significantly increased knowledge of risk/susceptibility to CRC and had an increased intention to undergo screening. Unfortunately, there was no significant change in perceived benefits of screening, barriers or self-efficacy in this discussion group compared to when they initially began the visit. Finally, a 6-month follow-up revealed that 45% of patients within the group that discussed CRC screening actually underwent screening, as compared to the non-discussion group in which no patient was screened.²⁷

DISCUSSION

Screening for CRC is an integral part of cancer prevention and has the capacity to positively impact CRC mortality rates. Colonoscopy has proven to be a leading method of CRC screening and its use has increased in many regions across North America.^{9,11} However, detection of CRC via colonoscopy does not occur uniformly within the colon, and specific 'burdens' of screening are discouraging individuals from participating in colonoscopy. Thus, prematurely accepting colonoscopy to be the superior screening modality is erroneous. Many factors must be considered when defining a tool as superior including patient preferences, user-dependent skills, success of CRC detection and cost-effectiveness. Until research can address these factors and clearly define superiority, the debate over which method to choose for CRC screening remains.

Unlike research on sigmoidoscopy and CTC, current scholarly literature analyzed in this study has not produced RCTs studying colonoscopy as a method of CRC screening. Many of the colonoscopy-focused studies analyzed in this review were observational (level 4) studies – a major limitation of this paper. Some studies lacked control groups, and their cohorts were often too small. In addition, each study focused

on only one or two screening modalities at a time, thus preventing grouped analysis of common variables. The initiation of RCTs with large cohorts comparing each specific modality in parallel and with more universal data analysis techniques is necessary. In addition, more prospective studies looking at the long-term benefits of colonoscopy are needed as current research shows many of the benefits of colonoscopy are observed several years following the initial procedure.¹¹ However, to accurately determine long-term benefits, studies must also focus on populations closer to the age of 50 as loss to follow-up due to death can negatively impact results.

Other limitations of this review included restricting search strategies with the filter 'full text available' during data collection and also focusing on only a select group of screening modalities. Studies on FOBT or FIT could have expanded the scope of this paper and enabled a more comprehensive comparison of all screening tools recommended by current guidelines.

Nevertheless, this paper addresses several important aspects of colonoscopy screening. First, a number of problems still remain in the actual effectiveness of colonoscopy screening. Many articles determined that colonoscopy was more beneficial in detecting distal CRC as opposed to proximal. Two RCTs identified that sigmoidoscopy also presented with similar caveats.^{18,19} Although both screening tools were limited in the location they could optimally perform, sigmoidoscopy proved to cause a greater reduction in distal CRC mortality as compared to colonoscopy. The PLCO trial found that mortality was reduced by 50% in the distal colon using sigmoidoscopy compared to colonoscopy,¹⁸ while the NORCAPP trial also identified that sigmoidoscopy's greatest reduction of mortality (76%) was seen for rectosigmoidal cancer (specific to the distal colon).¹⁹ Both values were higher than the 47% reduction in distal CRC mortality found via colonoscopy.¹¹ Identifying ways to optimize screening of both the proximal and distal colon is therefore necessary to enable colonoscopy to surpass the strengths of sigmoidoscopy.

Another major issue associated with colonoscopy was the variations in results due to the level of expertise of each colonoscopist. Gastroenterologists proved to be the most efficient when compared to surgeons and primary care physicians (Table 2). These performance differences can greatly impact the accurate detection of CRC and precancerous lesions. Furthermore, these differences in expertise may prevent the

significantly at-risk populations from being screened by the most skilled provider. Individuals from higher-income households ($> \$70,000$ compared to $\leq \$39,999$)²⁶ are more likely to take part in CRC screening, as a specialist appointment is more costly than a primary care visit. This is an unfortunate fact considering low income is a significant risk factor for CRC mortality.⁹ It is imperative that all health care professionals performing colonoscopies attain standardized training and continually strive to advance their skills so every patient can receive screening from an equally qualified colonoscopist. One way in doing so may be to increase attendance at CME meetings, as this had a positive association with ADR in primary care providers.¹⁴

In spite of the disadvantages of colonoscopy use, this screening modality is still the most sensitive and specific test for detecting CRC and precancerous lesions of all sizes. Studies comparing colonoscopy to CTC and sigmoidoscopy identified that the rank from highest to lowest for specificity and sensitivity was colonoscopy $>$ CTC $>$ sigmoidoscopy. Although CTC was the closest to colonoscopy in sensitivity and specificity for CRC, it was 20–30% less sensitive for lesions < 6 mm in size than colonoscopy. Thus, exclusive use of CTC over colonoscopy risks missing small lesions that can present similar threats of cancerous growth as large ones. As many articles have noted, this failure to detect small lesions forces patients to endure additional investigations via colonoscopy in order to identify all those that are missed. Patients thus become burdened with extra tests leading to unnecessary stress and worry.

Currently only 65.1% of the US population is up-to-date on screening for CRC as recommended by standard guidelines.⁷ Among studied populations, the major reason for participation in both colonoscopy and CTC was to identify precancerous lesions, while the main reason to not participate was the thought that the colonoscopy procedure would be unpleasant and the belief that a lack of symptoms did not warrant undergoing CTC. Furthermore, when looking at reasons to choose specific screening modalities patients also assumed colonoscopy screening to be more burdensome than CTC due to its preparation and unpleasantness. However, patients admitted that in the long run colonoscopy was less burdensome,²⁵ suggesting that patient expectations or beliefs may often be due to a lack of knowledge and guidance. Understanding the factors that shape a patient's views on CRC screening is essential in learning how to present

screening in a positive light and how to create educational material that may further empower patients to comply with guidelines.

Much research has shown that the most significant factor in promoting screening is the interaction between a physician and patient. In one study, discussions about the risks and benefits of CRC, options for screening and family history of CRC occurred in only 76% of patient–doctor meetings.²⁷ Nevertheless, of the group of patients whose physicians did make an attempt to provide educational information, 45% went on to take part in colonoscopy screening. This study highlighted the fact that a simple conversation can enable individuals to take action. If physicians take adequate time to have detailed discussions with all at-risk patients and eliminate any myths of the procedure, it is likely that participation in colonoscopy screening will significantly increase.

CONCLUSION

In conclusion, colonoscopy has proven to be the most sensitive and specific tool for CRC screening and has allowed for significant reductions in CRC incidence and mortality. In order to ascertain that colonoscopy is superior to sigmoidoscopy and CTC in all aspects of CRC such as effectiveness in detecting both distal and proximal CRC, convenience of screening, efficiency of screening and patient preference, a number of factors must be addressed. First, large-scale RCTs looking at all three screening modalities together must be initiated in order to understand the exclusive benefits of colonoscopy and to move away from observational studies that are clouding current research. Next, eliminating the weakness of colonoscopy in detecting proximal CRC is imperative in order to ensure that it provides the greatest advantage possible. In addition, in order to enable patients to understand the life saving benefits of colonoscopy, misconceptions and narrowed views about this modality must be thoroughly addressed. Empowerment can start within the doctor–patient relationship. Once patients become more aware of their health and more knowledgeable about all of the preventative procedures available to maintain their wellbeing, they may be more inclined to take action. Finally, performing colonoscopies must become a more standardized procedure. All colonoscopists should ideally learn the same techniques and have access to the same quality of screening tools to ensure that operant-dependent differences do not confound the results of colonoscopy screening.

Conflict of interest and funding: The author declares no conflict of interest.

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The Growth of Medical Student Opportunities in Global Health

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Since the establishment of the World Health Organization on April 7, 1948,¹ global health has grown in prominence and popularity among health care workers at all levels of training. International clinical rotation electives have been available to students for over half a century² and interest in these programs has risen steadily over the decades. During this period, many organizations established programs for students and faculty interested in global health research and service. In 2006, these organizations united under the WHO's Global Health Workforce Alliance to assist students and faculty in becoming more involved in global health activities.³ Despite these changes, in 2007, Drain et al. recognized a lack of global health education in medical schools and growing student interest, calling for more opportunities to fill the gap.⁴ Since then, nearly all US medical schools have created opportunities for students to engage in study or service on the international stage.⁵ The 2013 Association of American Medical Colleges survey of graduating US medical school students found that 30.2% of graduates participated in global health experiences,⁶ an increase of nearly 25% since the first Graduation Questionnaire was administered in 1978.⁵ A current search on the American Medical Student Association website for International Health Opportunities generated a list of 319 programs, including experiences through medical schools, governmental programs, and non-governmental organizations. The variety of opportunities allows students to serve in many different capacities, from hands-on clinical experiences to immersion learning of different languages.

Multiple surveys have shown that the majority of students who have participated in international experiences have had positive experiences and most would recommend these opportunities to their colleagues.⁷⁻⁹ Reviews and evaluations of these programs, however, have not all been positive. Concerns about the impact of medical missionaries have been raised, ranging from

the exploitation of the local population to the safety of the student participants.¹⁰ One analysis showed that some short-term groups may actually erode the health of the local populace due to the provision of sporadic care as well as 'quick fix' solutions that students can complete in their time there instead of more long-term options.¹¹ To help other programs address these concerns, Suchdev et al. devised a model for international health mission trips with guidelines to help ensure that such trips are able 'to ethically address underlying health issues and to provide sustainable public health interventions and medical assistance for underserved communities in developing countries.'¹⁰ In addition, the Working Group on Ethics Guidelines for Global Health Training (WEIGHT) drafted specific guidelines to help enhance the educational value of the programs and ensure the safety of patients and students.¹² The Association of American Medical Colleges also drafted their own guidelines in 2011 for students participating in international clinical experiences.¹³

Recently, a study examined the impact of short-term missions from the perspective of the patients. Patients from a short-term mission to the Dominican Republic were surveyed on issues ranging from language barrier to student involvement. These patients did not feel that their care was substandard. Also, the language barrier was not perceived to be an issue and student involvement, when well-supervised, was viewed as positive, with one interviewee stating, '[I feel] very good because when you are practicing on me you are studying. You need to practice because medicine is 50% theory and 50% practice.'¹⁴

Studies of global health experiences have also found many benefits to these short-term medical missions. As the patient population in the United States continues to diversify, cultural competency is becoming a more vital element of an effective physician. An understanding of cultural issues became an established part of medical education with the inclusion of 'interpersonal

skills' as one of the six core competencies established by the Accreditation Council of Graduate Medical Education in 2007. This requires that all residents be able to 'communicate effectively with patients, families and the public, as appropriate, across a broad range of socioeconomic and cultural backgrounds'.¹⁵ Language and cultural barriers can impair quality of care, particularly in low-income areas. While a week-long medical mission is not enough to overcome these barriers, one study showed that immersion in another culture in the form of study abroad fostered a stronger ability to interpret the behaviors of others in a broader cultural context,⁹ teaching students how to ask the right questions when confronted with cultural differences and enhancing their ability to view patient behaviors in the proper cultural context. A literature review of international health electives in medical school also found that participants had a deeper understanding of global and public health issues, scoring higher on these sections on National Board of Medical Examiners (NBME) examinations.¹⁶ As an added benefit, the review indicated that participants were more likely to go into primary care fields and work in underserved areas,¹⁶ providing a potential source of primary care providers to ease the worldwide shortage.

Combining clinical training with an exploration of global health issues, short-term medical missions are a unique opportunity for medical students to develop their clinical skills and deepen their understanding of social and cultural issues in medicine. As patient populations grow increasingly diverse, an understanding of cultural and global issues in health care is becoming an essential component of medical education. Participating in international health missions allows students to develop a stronger understanding and gain a personalization of these issues, enhancing the social acumen of future clinicians and raising the level of debate in the discussion of global health issues. In response to the many early criticisms of these programs, there has been an outpouring of research supporting the efficacy of these programs and highlighting the positive responses from both patients and students. Multiple studies on the effectiveness and impact of these programs have unmasked many of the risks, and guidelines have been established to address these issues. However, continued evaluation would not be remiss to further strengthen these programs and ensure patients and students get the most out of these beneficial, and costly, experiences. The development of these programs over the years has grown international medical missions into a popular pedagogical tool that also serves to inspire students to

further explore cultural, primary care, and global health issues. With an ever-growing need for international health workers and an increasingly diverse patient population, it is time for international health experiences to grow from an extracurricular activity into an integral part of medical education.

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