

THE HARVARD MEDICAL STUDENT REVIEW

ISSUE 2
JANUARY 2015



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From the Editors' Desk

January 6, 2015

Dear Colleagues,

We're excited to announce the second issue of the Harvard Medical Student Review! We're proud of the original research, opinion pieces, comments on medical education and health policy, and artwork from a variety of authors and artists. Three major pieces of groundwork made this issue possible.

First, we developed a rigorous peer-review process. Over the past five months, each article underwent double blind reviews by students with training, interest, or education in the relevant field. We believe this process is responsible for the quality of the articles and is a vital part of the Review's evolution.

Second, the true power behind this peer review system was the dedication of our associate editors. They went above and beyond what could be reasonably expected from medical students and worked hard to make their comments insightful, constructive, and compelling.

Third, we owe so much to our founders. Shattered mugs or otherwise, they are the reason this publication exists. From the contacts, to the administrative hurdles, to the audacity of the idea for the Review: their sheer jubilation has been infectious and motivating.

We hope you enjoy the Review!

Mark McElroy
Eric Robbins
Arthur Bartolozzi
Leigh Ann Humphries

PS Submissions are open for the next issue!

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Article

Dr. Maiden Name Will See You Now

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Synopsis: Women doctors often decide whether to adopt a husband's name after they have developed professional and personal identities with their maiden names. This article presents the results of a survey taken by women in the second-year class at Harvard Medical School regarding the use of their maiden names after marriage. Two nationally renowned doctors, Dr. Elizabeth Nabel and Dr. Ardis Hoven, also commented on the survey's findings and discussed factors that influenced their personal decisions to "keep" or "change."

"Dr. Lewis is on call tonight... Dr. Stevens will see you now... Good morning, Dr. Quinn..." We are used to addressing doctors by their last names. These names are often associated with authority and reputation in the hospitals and throughout academic communities. They mark groundbreaking inventions and discoveries, such as *Alzheimer's* disease, *Down's* syndrome, *Apgar* score, and *Foley* catheter. All of this focus on the last name is particularly relevant to young women entering the field of medicine. Most female medical students, including myself, are unmarried and will begin their careers with their maiden names. Many of us have imagined how our last names will sound with the title of "Dr.," much like a bride-to-be might admire her future name with "Mrs." Interestingly, the present study suggests that, unlike the general population, most future female doctors at Harvard Medical School have plans to keep their maiden names after marriage, especially if they marry later in their careers (Kopelman et al., 2009).

Choosing what to do with a maiden name can be more complicated than one might think. Some powerful women in the U.S., such as Janet Yellen, Sheryl Sandberg, and Marissa Mayer, have kept their maiden names after marriage, while others, like Melinda Gates, Virginia Rometty, and Indra Nooyi, have built empires after taking their husbands' names. Hilary Rodham Clinton has kept her maiden name in the spotlight as a middle name, and Beyoncé Knowles-Carter chose a hyphenated name, but occasionally identifies as "Mrs. Carter." Some women even choose "name blending," in which the husband and wife combine both last names into a new one. The option a woman chooses does not necessarily reflect her political or religious views, as was once thought. One woman's name choice might represent strongly held feminist beliefs, while another might be simply convenient or aesthetically pleasing.

Women who do decide to keep their maiden names are anything but maidens. Many are high-power executives, news anchors, lawyers, artists, or as this article suggests,

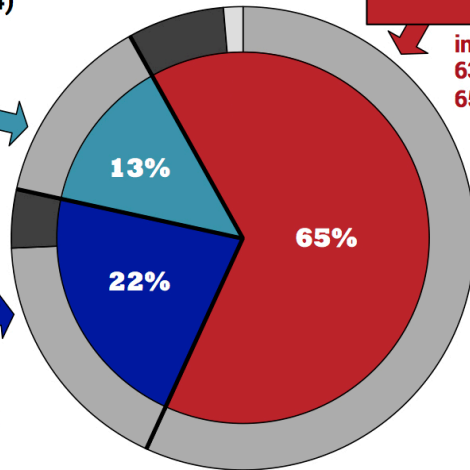
future leading doctors. Highly educated, high-earning women are disproportionately likely to keep their names after marriage (Kopelman et al., 2009). This may not be surprising. Long education and competitive work environments lead some to marry at older ages, at times when they have established professional and personal lives with their maiden names. Greater women's autonomy and changing gender norms have made women today more equal partners in marital relationships, both socially and financially. This climate is very different from the one in England a few centuries ago, where the tradition of changing surnames originated. Laws restricting women's ownership of property caused them to take their husbands' names to maintain ties to his estate (Anthony, 2010). Over the years, this custom has become embedded in American culture and even its legal system. State laws requiring women to adopt their husbands' names in order to exercise basic privileges, such as voting and maintaining a driver's license, have only been struck down as recently as 1975 (Emens, 2007).

The majority of women in the U.S. today still change their names. Nonetheless, the percentage of women keeping their maiden names has risen in recent decades from 1% in the 1970s to 9% in the 1980s to about 20% in the 1990s and 2000s (Kopelman et al., 2009). The rate of "keeping" further doubles when you look at Harvard University alumnae, specifically. More than 50% of the women in the Harvard College Class of 1980 who married in the 20 years after graduation kept their maiden names, and those who pursued advanced degrees or married and had children in later years were most likely to keep them (Goldin and Shim, 2004). In fact, Harvard women with a Ph.D. or an M.D. had about a 25% lower probability of changing their names than did those with no advanced degrees. The overall likelihood of changing one's name also declined by about 1 percentage point for each year of marriage delay and 1.3 percentage points for each year of delay in having children (Goldin and Shim, 2004).

**Harvard Medical School
Class of 2017 (n=74)**

**13% preferred to
adopt joint or
hyphenated names**
including:
15% of single women

**22% preferred to
adopt their
partners' names**
including:
37% of married women
20% of single women



**65% preferred to keep their
maiden names**

**including:
63% of married women
65% of single women**
(40% *Regardless of when they marry*)
(3% *If married during med school*)
(13% *If married after med school*)
(9% *If married while in practice*)

Single
Engaged
Married

Figure 1. Most women at Harvard Medical School preferred to keep their maiden names after marriage.

Seventy-four women in the Class of 2017 responded to surveys and were either already married or wished to marry in the future. The great majority of single, married, and engaged women wanted to keep their maiden names after marriage. Some single women also said their decisions depended on when during their careers they married. Other name choices were less common with 22% preferring their partners' names, and 13% preferring joint or hyphenated names.

Recognizing the long-term educational and career goals of female doctors, I decided to ask women at Harvard Medical School about their plans for their surnames after marriage using an online survey (Suppl Figure 1). Of the 75 women (ages 22-35) in the Class of 2017 who responded to surveys, 8 (11%) were married, 1 (1%) was engaged, and 66 (88%) were single. All single women except for one wished to get married in the future. The desire to keep one's maiden name after marriage was very common; 65% of the single women wished to keep their maiden names, and 63% of the married women had already chosen to do so (Figure 1). Also, 40% of the single women wished to keep their names regardless of when they married, while 25% said that the timing of marriage could affect their decision. Most felt that marrying later in medical training would make it more likely for them to hold onto their maiden names.

Among women who preferred to keep their maiden names, personal identity was very important (Figure 2A). One woman said, "I would like to feel that I am still my own person, not an object possessed by my spouse." Others conveyed a similar sense of indignation toward the long-held tradition of giving up surnames: "women are of equal value to men and should not be treated as a possession (e.g. by being named)." Many also felt that their last names connected them to "cultural and familial roots." They discussed their affiliations with various cultures and countries of origin, in which it is customary for women to keep their names after marriage. Another simply asserted, "Brand loyalty." Still others focused on the accumulation of publications and professional contacts with their maiden names, citing "professional continuity" as a primary reason.

By contrast, women who wanted to adopt their husbands' names considered their relationships with

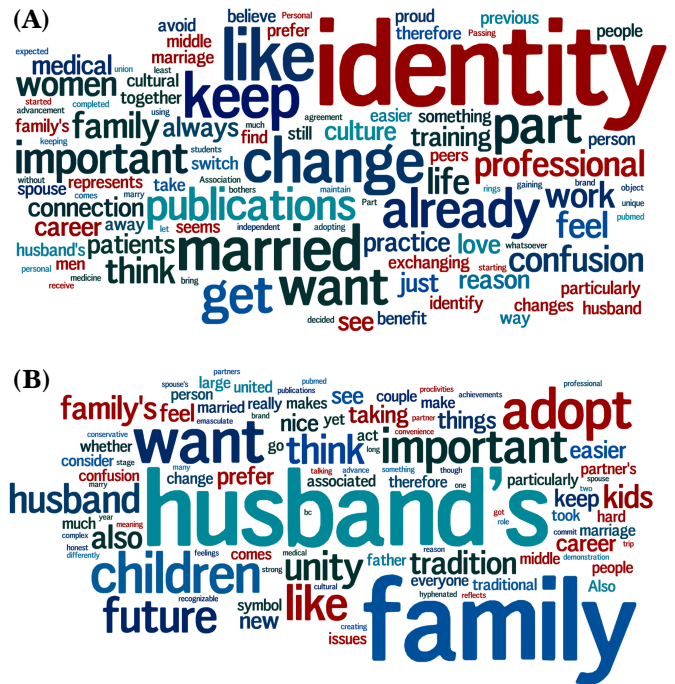


Figure 2. Medical students tended to use similar key words in explaining their preferences.

- (A) Words used in response to: "If you would prefer to keep your maiden name at any stage, why is this important to you?"
- (B) Words used in response to: "If you would prefer to adopt a new last name at any stage, why is this important to you?"

Eighty-nine percent of the women surveyed gave free-response answers explaining the reasons for their name choice. Two word clouds display the relative prominence of the words used in their responses. Since almost all responses to both questions used "maiden," "last," and "name," these three words were removed to showcase other words.

their future husbands and children to be a central focus (Figure 2B). Most viewed the name change as a “demonstration of unity” within the new family. For one woman, the act functioned “to ensure familial continuity between myself and my children, and to adhere to my spouse’s wishes when I don’t consider this a large sacrifice.” Most women also felt that it was simply “easier” for husband, wife, and children to have the same name. Different names or hyphenated names can become complicated and create confusion for their children. A few women also discussed the absence of a close or loving biological father in their lives, and as a result they looked forward to giving up their maiden names and adopting a new one. Only one woman cited strong conservative ideology and tradition as her reasons for changing her name.

To gain further insight into the decision process, I spoke with two powerful women in U.S. health care, Dr. Elizabeth Nabel and Dr. Ardis Hoven, who described their personal decisions regarding their maiden names and explained the broader context of the study’s findings. Both women are known nationally for their contributions to the medical field in clinical, academic, policy, and administrative spheres. Interestingly, they both chose opposite paths for their maiden names.

Dr. Elizabeth “Betsy” Nabel, the current President of Brigham and Women’s Health Care in Boston, MA, discussed multiple reasons for taking her husband’s name. She made this choice despite marrying in her 30s, after her senior year of residency, with multiple publications and accolades to her name. She explained that her maiden name, Guenther, had been difficult for her patients to pronounce, spell, and remember; Nabel, on the other hand, was easy and appealing because it provided her family with “one central name.” In addition, Dr. Nabel’s story showed how decisions about surnames are often made in collaboration and in the context of other important family traditions like religion, education, and culture: “I come from the Midwest and was raised with very traditional values. My husband comes from a family of Holocaust survivors. We wanted to honor our backgrounds and traditions, so we agreed that I would take his name.” Dr. Nabel also understood how the issue of identity might be critical to women in their 20s, but stated that as a 32-year-old, her name was not a big part of her identity: “Who you are as a person is somewhat independent of a name. [...] As I progressed in my skill acquisition, competencies, knowledge, and confidence, I was secure in my identity as a physician, first and foremost.” She advised from a logistical standpoint that immediately after the name change, it helped to include her maiden name as a middle name on her CV. She insisted though that the transition was easy for her colleagues and patients alike, especially because her husband was also a resident at the same hospital. She said, “It was expected that I would come back from my honeymoon with the name Nabel.”



Elizabeth G. Nabel, M.D.

*President of Brigham and Women’s Health Care
Professor of Medicine at Harvard Medical School
Former Director of the U.S. National Heart, Lung, and Blood Institute*



Ardis D. Hoven, M.D.

*Immediate Past President of the American Medical Association (AMA)
Member of the AMA Board of Trustees since 2005
Past President of the Kentucky Medical Association*

Figure 3. Photographs and select positions of distinction held by Dr. Nabel and Dr. Hoven.

Dr. Ardis Hoven, the immediate past president of the American Medical Association, took a different route; she kept her maiden name. According to Dr. Hoven, choosing whether to keep or change one’s name is a common dilemma faced by women in medicine. In fact, she stated that the distribution of preferences found in my survey was “comparable” to what she has observed among her female colleagues at the local and national level, with most women choosing to keep their maiden names. She said that women doctors today are more comfortable choosing to maintain their names than they were 20 or 30 years ago. She added, however, in accordance with this study’s findings: “It really depends on how old they are and where they are in their careers when they get married.” With regard to Dr. Hoven’s own decision to keep her name, she explained, “I married fairly late. My career had already been established. I had leadership in the state medical association, in my county, and also in my practice. I was recognized by that name as someone providing a particular health care service. Changing [my name] at that time would have been disruptive—not impossible, but disruptive.” She mentioned how her practice had been set up under her maiden name, even the letterheads. In addition to these advantages for her professional life, she felt personally connected to her maiden name and shared sentiments similar to those of many medical students: “I also like my maiden name. People tend to remember it. I’m also extremely proud of my heritage; my grandfather on my dad’s side immigrated from Sweden.” Of course, it also helped that her husband “didn’t have any problem with it at all.” Similar to Dr. Nabel, there are common themes that affected Dr. Hoven’s preferences about her name, including identity, age, family, and heritage, as well as her husband’s voiced opinions.

The data and commentary presented in this article point to several key conclusions. First, women in and entering the medical profession are more likely to make non-traditional decisions about the use of their maiden names after marriage. In the Class of 2017 at Harvard Medical School, the vast majority of women expressed preferences to keep their maiden names, and a significant percentage also desired joint or hyphenated names. Of course, most women surveyed at Harvard Medical School were single, and therefore, the inability to predict future partners' preferences could have skewed the results in favor of "keeping." The anonymous nature of survey, however, allowed women to express their personal preferences freely, without the risk of social stigma or opposition from significant others. Also, the reasons given for a certain name choice went beyond notions of a professional brand or career continuity; both Harvard medical students and Dr. Hoven additionally cited personal identity and ties to family or heritage as primary motivators for keeping a maiden name. Of note, the students almost never referred to conservatism or tradition as reasons to adopt a partner's name, in contrast to Dr. Nabel's reasons and those documented in previous studies (Twenge, 1997). Rather, they focused primarily on pragmatic concerns for children and family.

So why does this question about maiden names matter? First, the sheer magnitude of the number of women who discuss and consternate over this decision, whether or not they are engaged, make it worth recognizing and illustrating. To my knowledge, this is the first study in the medical literature to address the preferences of women doctors regarding the use of their maiden names.

Also, most importantly, a woman's name influences the way people perceive her. Our society places a great deal of importance on names as symbols of identity, selfhood, and status. The name that a woman chooses after marriage may further elicit certain stereotypes. One study found that women who took their husbands' names were perceived as less agentic (e.g. less ambitious) and more communal (e.g. kinder, more nurturant) than women who either kept their maiden names or hyphenated their names (Etaugh et al., 1999). Another study reported that women with hyphenated names were thought to be more friendly, good-natured, industrious, career-oriented, and intellectually curious, compared with the average married woman (Forbes et al., 2002). These studies are likely outdated and non-generalizable, but thought provoking nonetheless.

Ultimately, there is no universally correct decision about a maiden name, and women may benefit from information and advice shared by others with similar experiences. My choice not to endorse my own opinions about the future use of my maiden name is deliberate. The intent of this article is not to sway readers one way or another, but to highlight an interesting phenomenon

in the medical community and to provide an outlet for discussion. It is clear that a woman's decision to keep or change her name is a personal one, with determinants that vary from person to person.

Acknowledgements

Special thanks to Dr. Elizabeth Nabel and Dr. Ardis Hoven for providing critical insights on the study's findings and for sharing their personal stories. Also, thanks to Dr. Sushrut Jangi of Beth Israel Deaconess Medical Center for his gracious mentorship and assistance in reviewing and revising this manuscript.

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Article

The Most Common Illness: A Review and Case Study from Harvard Medical School

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Synopsis: The average adult experiences two to five common colds each year. Summed up, people spend more than a year of life suffering from the illness. This article presents a brief report from an outbreak at Harvard Medical School followed by a review of what is currently known about the common cold. An emphasis is placed on illustrative experiments. Despite decades of research, hand washing remains the best method for preventing infection.

Case Study

In August and September of 2014, there was an outbreak of an acute respiratory infection (ARI) among the first and second year students at Harvard Medical School and Harvard School of Dental Medicine. Out of 400 students, 74% (296) completed an anonymous retrospective survey concerning their recent health. Of the respondents, 34% of second year (57 of 167) and 25% of first year (33 of 129) students reported experiencing an acute illness over the preceding month. 94% (278 of 296) of the recently ill students reported experiencing one or several ARI symptoms, including nasal congestion, cough, sore throat, and nasal discharge. Incidence data were compiled from self-reported dates of when respondents first began feeling ill (Figure 1).

Behaviors Associated with Infection

The survey also asked respondents five questions concerning recent social behaviors. Relative risks of becoming ill were calculated for these dichotomous behavioral variables, both as a complete cohort and after stratifying the respondents based on class year (Table 1). Among both classes, the only two risk factors found to be significantly associated with becoming ill were recently going to a party or bar with classmates (RR 1.45, 95% CI 1.000 to 2.104, $p = 0.0497$) and frequently or always studying with classmates (RR 1.48, 95% CI 1.010 to 2.188, $p = 0.0444$). None of the other behaviors queried significantly altered the risk of contracting an acute illness.

Infectiousness

Kermack and McKendrick's compartmental epidemiological model was used to calculate the basic reproduction number R_0 for the outbreak under the assumption that ill medical students were infected by their classmates (Kermack and McKendrick, 1991). For the combined classes, R_0 was calculated to be 3.5,

indicating that the average ill student infected 3.5 of his or her classmates. By way of comparison, estimated R_0 for other infectious diseases include 2.7 for the 1918 A/H1N1 influenza pandemic (Mills et al., 2004), 1.5 for the 2009 H1N1 pandemic (Yang et al., 2009; Fraser et al., 2009), 3.6 for the 2003 SARS outbreak (Wallinga and Teunis, 2004), and 1.73–2.02 for the 2014 Ebola virus epidemic (WHO Ebola Response Team, 2014).

Behavioral Model of Disease Transmission

The probability of illness transmission is proportional to the product of the number of contact events sufficient for transmission between individuals and the per-event likelihood of transmission. Kermack and McKendrick's compartmental model treats populations as homogenous and combines these two factors into a single parameter that represents the transmission rate across the population. This approach is useful for large populations where following individual interactions are impractical or when no information on social network structure is available. While this model can predict the total number of individuals who will be ill at a given time, it neither gives any information on how illnesses are dispersed among subsets of the population nor provides the opportunity to use behavioral data to predict transmission.

This study had both a small population and limited behavioral data. These allowed for the construction of a discrete-time Markov model of disease transmission through the class, wherein probability of a transmission event between any pair of students was proportional to the behavioral similarity of the pair. Ideally, such a behavioral model has the advantages of allowing a better prediction of the spread of disease prospectively and an understanding of the specific social interactions that promote disease transmission retrospectively. Unfortunately, in the current study, the model informed

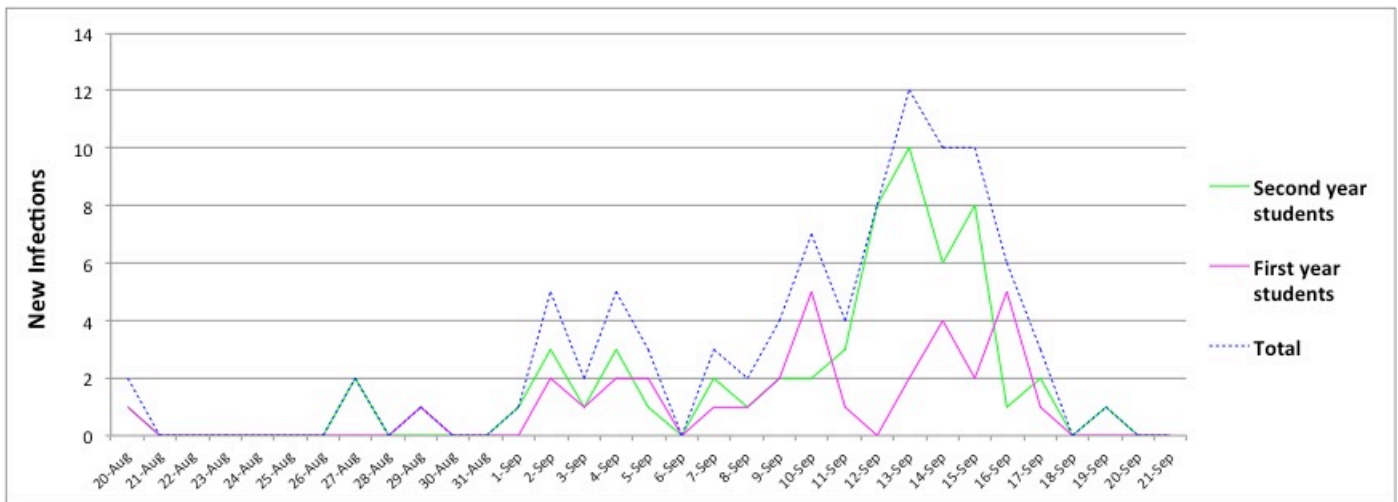


Figure 1. Incidence from Outbreak at Harvard Medical School

Among the 296 respondents to a retrospective survey, 90 students (30%) reported symptoms of an acute illness over a month-long period. 34% of second-year (57 of 167) and 25% of first-year (33 of 129) medical and dental students reported experiencing an acute illness over the previous month.

Survey Question	Sick Respondands Answering "Yes"	Healthy Respondands Answering "Yes"	Relative Risk of Activity (95% CI)
Going to a Bar/Party with Classmates in Last Week			
<i>First year</i>	58%	55%	1.074 (0.591 to 1.950)
<i>Second year</i>	66%	45%	1.784 (1.106 to 2.879)*
Total	63%	50%	1.451 (1.000 to 2.104)*
Living in Medical School Dorm			
<i>First year</i>	82%	84%	0.875 (0.412 to 1.854)
<i>Second year</i>	36%	42%	0.843 (0.529 to 1.342)
Total	53%	62%	0.791 (0.555 to 1.127)
Time Spent in Medical Education Building >30 min Daily			
<i>First year</i>	42%	47%	0.874 (0.412 to 1.854)
<i>Second year</i>	28%	39%	0.715 (0.432 to 1.183)
Total	34%	43%	0.761 (0.520 to 1.114)
Studying with Classmates, Sometimes or Always			
<i>First year</i>	70%	65%	1.191 (0.623 to 2.274)
<i>Second year</i>	66%	45%	1.784 (1.106 to 2.879)*
Total	67%	54%	1.487 (1.010 to 2.188)*
Attending Most or All Lectures			
<i>First year</i>	85%	76%	1.552 (0.661 to 3.649)
<i>Second year</i>	60%	59%	1.037 (0.659 to 1.631)
Total	70%	67%	1.096 (0.742 to 1.617)

Table 1. The Relative Risks of Contracting an Acute Illness from Various Dichotomous Behaviors

Data were calculated from anonymous surveys to medical and dental students, and relative risks calculated for first- and second-year classes, as well as in total. Among both classes, going to a bar or party with classmates in the last week and studying with classmates some or all of the time significantly increased the risk of contracting the illness. For both classes, living in the medical school dorm, spending more than 30 min a day in the medical education building, or regularly attending lecture did not significantly alter the risk of becoming ill.

by social behavior did not predict the spread of illness any better than Kermack and McKendrick's compartmental model. This is likely because the behavioral survey lacked the granularity to adequately capture pairwise social interactions. The behavioral variance calculated from survey responses was small across the population, and students who reported similar behaviors may not have preferentially interacted with one another. In future studies, capturing data more descriptive of pairwise interactions—for example, via construction of a social network wherein network distances are taken to be the probability of interaction sufficient for transmission—may allow this method to be used to build an informative model of disease spread in a small population.

Other Considerations

The magnitude of this outbreak was larger than would be expected based on prior studies of ARI's among small communities in relative isolation (Warshauer et al., 1989; Flynn et al., 1977). The identification of a pathogen is not required to diagnose the common cold, but it is possible that the pathogens responsible for this outbreak were heterogeneous in nature (Heikkinen and Jarvinen, 2003). While informal studies such as this may intuitively seem as if they can inform medical students who wish to avoid catching a cold during the school year, classic and contemporary research has unraveled more profound insights into common cold pathogenesis, transmission, and prevention

Introduction

How Common is the Cold?

Cohorts of medical students have or likely will experience occasions when a mysterious ARI rapidly sweeps through their flu-vaccinated class. The common cold is a mild ARI characterized by some combination of malaise, rhinorrhea (nasal discharge), nasal congestion, headache, cough, sneezing, sore throat, and low-grade fever (Jackson et al., 1958). While the cold is unfortunately considered “low yield” for USMLE Step 1 purposes, respiratory infections are the most common cause of illness in industrialized countries (Denny, 1995) and are likely the most common cause of illness worldwide (Papadopoulos, 1999). Adults have two to five colds per year, totaling in a lifetime to over a year spent with the disease (Papadopoulos, 1999; Johnston et al., 1996). Twenty-five million patients in the US visit the doctor with an ARI chief complaint every year, resulting in \$726 million spent on unnecessary antibiotic prescriptions (Gonzales et al., 2001). One study found that 76% of elderly patients with viral common colds were prescribed antibiotics (Nicholson et al., 1996). The 500 million domestic cases of non-influenza ARI's directly cost the US healthcare system \$17 billion annually (Fendrick et al., 2003). By comparison,

influenza has a direct medical cost of \$10.4 billion annually (Molinari et al., 2007). The cold is a significant source of lost productivity as well (Molinari et al., 2007), causing adults in the US to miss 20 million days of work annually (Adams et al., 1996), with indirect costs of \$22.5 billion (Fendrick et al., 2003).

Relevance to Doctors in Training

Given the absence of effective treatments or means of diagnosis, the common cold remains pertinent to medical students because unintentionally transmitting an ARI to any of several vulnerable patient populations with whom medical students interact can significantly raise a patient's risk of death (Meibalane et al., 1977; Strausbaugh et al., 2003; Malavaud et al., 2001; Horcajada et al., 2003; Dolan et al., 2012). Infection with the cold can cause asthma and chronic obstructive pulmonary disease (COPD) exacerbation, frequently leading to hospitalization (Nicholson et al., 1993; Mallia et al., 2011; Teichtahl et al., 1997). For immunocompromised individuals, the cold can mean serious complications and possibly death (Ghosh et al., 1999). Even among elderly patients, a cold lasts twice as long, has more severe symptoms, and has double the risk of a lower airway complication such as pneumonia (Nicholson et al., 1996, 1997).

Despite the prevalence and economic impact of the disease, the common cold is not proportionally emphasized in medical education. An understanding of the cold is needed to refrain from prescribing patient's unindicted antibiotics, and, in lieu of effective treatments, medical providers should know the proven preventative measures. By understanding the fundamental features of common cold transmission, medical students can significantly lower the chances that they spread the infection (Jefferson et al., 2011). Such an understanding will contextualize asthmatic and COPD patients who present in the emergency room short of breath following an otherwise-harmless cold (Teichtahl et al., 1997). By learning about the cold, a prudent student can also minimize his or her own productivity lost to illness as well. Finally, insights into mankind's most common infection can help one understand and contextualize more malicious infectious diseases.

Causes

Viral Distribution

The common cold does not have a single cause. Rather, the cold is caused by a host of viruses with strikingly diverse phylogenetics (Figure 2). Across all age groups, the most common cause of the cold is the rhinovirus, accounting for around half of common cold infections (Monto and Sullivan, 1993). The rhinovirus displays season-dependent transmission, and during its peak in autumn, the pathogen causes up to 80% of colds (Arruda

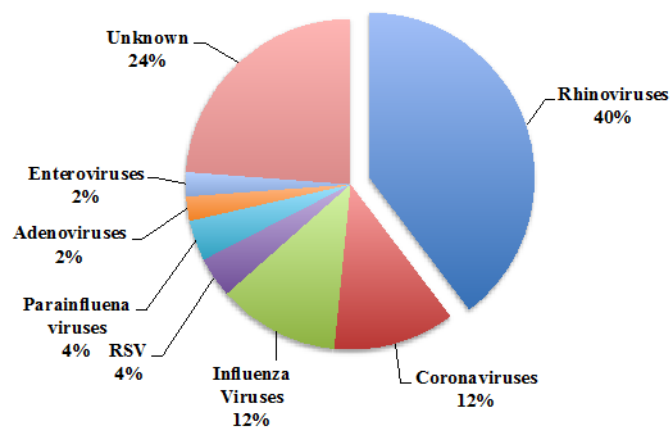


Figure 2. The Proportion of Common Cold Cases Caused by Each Type of Virus

The cold is caused by a diverse arrangement of viruses. Approximately one out of four common colds have an unknown cause, and there are likely still undiscovered viral pathogens (van den Hoogen et al., 2001). The numbers shown above change throughout the year as most of the viruses associated with the common cold display seasonality. For example in the autumn, the 100 serotypes of the rhinovirus can cause up to 80% of common colds (Arruda et al., 1997). Data adapted from Heikkinen and Jarvinen (2003).

et al., 1997). Together the coronaviruses, respiratory syncytial viruses (RSVs), and parainfluenza viruses, adenoviruses and enteroviruses account for around 35% of colds (Fendrick et al., 2003). Influenza viruses cause around 5%–15% of colds. Because the common cold is defined on the basis of its clinical presentation, a mild influenza infection can accurately be diagnosed as a cold, meaning that the two infections are not completely distinct disease entities (Heikkinen and Jarvinen, 2003). It is suspected that yet-unidentified viruses explain the remaining 20%–30% of the cases of the cold. For example human metapneumovirus has a worldwide distribution but was only discovered in children with the cold in 2001 (van den Hoogen et al., 2001).

Rhinovirus and ICAM-1

As rhinovirus is the most frequent cause of the common cold (Monto and Sullivan, 1993), the pathogen will be the primary focus of this review. The rhinovirus infects epithelial cells of the nasopharynx. Viral particles gain access to the epithelium by the mouth or nose or from eyes via the lacrimal duct (Hendley, 1999). The eyes and nose are the most common routes of inoculation (Hendley et al., 1973). It is known neither how the rhinovirus gains direct access to cells within the nasal mucosa nor if the rhinovirus can infiltrate an intact mucosal membrane (Winther, 2011). 90% of rhinovirus serotypes enter epithelial cells in the nasopharynx after

binding the surface protein ICAM-1 (Greve et al., 1989). This receptor is selectively expressed by certain epithelial cells, with a high concentration among non-ciliated epithelial cells of the nasopharyngeal tonsil (adenoid) (Teichtahl et al., 1997). Successful rhinovirus infection leads to an upregulation of ICAM-1 and downregulation of an endogenous decoy ICAM-1, thereby enhancing the viruses' infectivity (Whiteman et al., 2003). Rhinovirus can spread from a simple ARI and infect epithelial cells in the lower airway as well (Papadopoulos et al., 2000). Subsets of epithelial cells in the lower airway also express ICAM-1, though at a lower density than in the upper airway (Mosser et al., 2002). The optimal temperature for rhinovirus replication is 33°C–35°C (Hayden, 2004). In healthy adults, the nasopharynx temperature is usually 34°C (Keck et al., 2000). Despite being deeper in the body, areas of the lower respiratory tract fall within rhinoviruses' replication range as well. For example, the carina is 33.2°C during normal breathing (Hayden, 2004). Among infants, rhinovirus is the second most common cause of pneumonia and bronchiolitis, largely due to its ability to infect the lower airway (Hayden, 2004).

ICAM-1, Asthma, and Clinical Symptoms

Epithelial ICAM-1 expression is upregulated following inflammation and mediates subsequent neutrophil migration (Vejlsgaard et al., 1989; Smith et al., 1988). As asthma is a disease characterized in part by bronchial inflammation, patients with asthma tend to have basally elevated ICAM-1 expression levels in the lower airways (Wegner et al., 1990). This potentially explains the strong association between cold infections and acute asthma exacerbations. Rhinovirus infections in asthma patients are known to cause morbidity and sometimes mortality (Johnston et al., 1996). It is estimated that between 50%–80% of asthmatic exacerbations are caused by the cold (Johnston et al., 1995, 1996). One study found that 37% of patients who required hospitalization for an acute asthma attack had a viral ARI (Teichtahl et al., 1997). Hospital admission is for asthma patients the strongest predictor of 12-month mortality (Crane et al., 1992). A laboratory infection of 13 non-asthmatic volunteers with COPD showed that rhinovirus infection leads to COPD exacerbation and lower respiratory symptoms, though the role of ICAM-1 in these patients is less clear (Mallia et al., 2011).

Interestingly, 25% of patients infected with a cold-associated virus remain clinically asymptomatic (Gwaltney and Hayden, 1992). Adults are more likely to remain asymptomatic during an infection than children (Peltola et al., 2008). Children also have more severe colds. Among children, 70% have colds that last at least 10 days (Pappas et al., 2008), as opposed to only 20% of adults (Gwaltney et al., 1967). It has been proposed that acquired immunity and variations in ICAM-1 expression with age may explain why some individuals have active

viral infections but remain asymptomatic (Peltola et al., 2008). One study found that polymorphisms of ICAM-1 were associated with varying susceptibility to common cold illnesses (Nieters et al., 2001). However, common cold cases in this study were self-reported, and it is unclear if individuals with “protective” ICAM-1 genotypes were more likely to resist initial infection of epithelial cells or if infected individuals were more likely to remain asymptomatic. Still, ICAM-1 remains a promising target for future research aimed at preventing rhinovirus infection.

Symptoms

Clinical Presentation

Because of the variation in clinical symptoms that patients with a common cold experience, it has not been possible to develop a pathognomic characterization of the disease (Eccles, 2005). Diagnosis is made clinically from reported symptoms with good reliability (Heikkinen and Jarvinen, 2003). Nine out of ten patients who diagnose themselves with the cold are found to have an identifiable virus (Arruda et al., 1997). Experimentally, there are eight classic symptoms of the cold: sneezing, malaise, headache, chilliness, nasal discharge, nasal obstruction, cough, and sore throat (Jackson et al., 1958). Not all of these are present in every patient with a cold, and a physical exam may sometimes reveal conjunctiva injection (bloodshot eyes) and pharyngeal erythema (<http://www.uptodate.com/contents/the-common-cold-in-adults-diagnosis-and-clinical-features>).

Time Course of Symptom Progression

Clinical symptoms tend to occur at overlapping but consistent time points during the course of an illness (Figure 3). Though incubation period depends to a large extent on the type of virus causing the cold (Bradburne et al., 1967), patients usually begin experiencing their first symptoms 24–72 hr after exposure (Heikkinen and Jarvinen, 2003). Classically, patients experience a sore throat 1 to 2 days after exposure, and the percent of patients experiencing a sore throat quickly dissipates after day 2 (Tyrrell et al., 1993). Patients then experience nasal discharge and obstruction between days 2 and 5, which gives way to cough by about day 6 post-exposure (Jackson et al., 1958; Tyrrell et al., 1993). On average, symptoms in healthy adults tend to spontaneously resolve after 7–10 days, with the cough generally being the last symptom to resolve (Heikkinen and Jarvinen, 2003).

In contrast, symptoms in elderly patients can take twice as long to resolve (median 16 days), and the risk of lower airway involvement is doubled (Nicholson et al., 1996). Children have the cold for longer as well, with most cases lasting at least 10 days (Pappas et al., 2008).

Children also tend to have slightly different symptomatic progression than adults. One study found 88% of children with the cold experienced nasal congestion and 75% nasal discharge on day 3 of illness—which is similar but more prevalent than in adults—but with cough peaking earlier on day 2 and remaining in half of children through day 8 of illness (Pappas et al., 2008).

Pathogen Identification

When narrowing down a differential diagnosis, the cold can be distinguished from similar illnesses on a clinical basis. Simple rhinitis will not present with a sore throat or cough, and bacterial tonsillitis will not present with a runny nose or nasal obstruction (<http://www.uptodate.com/contents/the-common-cold-in-adults-diagnosis-and-clinical-features>). The cold rarely presents with a high fever, the presence of which along with cold-like symptoms is suggestive of the flu. During periods of high flu activity, the CDC recommends that patients with this clinical presentation be rapidly triaged to minimize potential influenza exposure to healthcare workers and other patients (<http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm>). Pertussis may initially present as a common cold would, but coughing will persist for more than 2 weeks, and there may also be apnea or vomiting present (<http://www.uptodate.com/contents/the-common-cold-in-adults-diagnosis-and-clinical-features>).

Both the common cold and acute bacterial rhinosinusitis can present with purulent nasal discharge (thick, colored) (Wald et al., 1991). Sputum color is indicative of an inflammatory response but not of any specific pathogen (Eccles, 2005). Hence when clinically assessing an ARI, sputum color is a poor prognostic tool for determining whether antibiotics ought to be prescribed (Murray et al., 2000). Antibiotic treatment is indicated when a clinical diagnosis of acute bacterial rhinosinusitis is made on the basis of severe maxillary pain in the face or teeth, particularly if the pain is unilateral, and fever, or rhinosinusitis symptoms and maxillary pain lasting more than 7 days (Hickner et al., 2001). However the majority of acute rhinosinusitis cases that last fewer than 7 days will resolve spontaneously, and antibiotics ought to be withheld (Hickner et al., 2001).

While the cold-associated viruses can be individually identified using PCR assays, because the infection is typically benign and self-limiting, such identification is not medically indicated. Each family of viruses has slight variations in its presentation and pathogenesis. For example, one study found that 40% of patients with PCR-confirmed rhinovirus infections initially presented with a sore throat, but only 25% of rhinovirus-negative patients had this initial presentation (Arruda et al., 1997). However, accurately differentiating the common

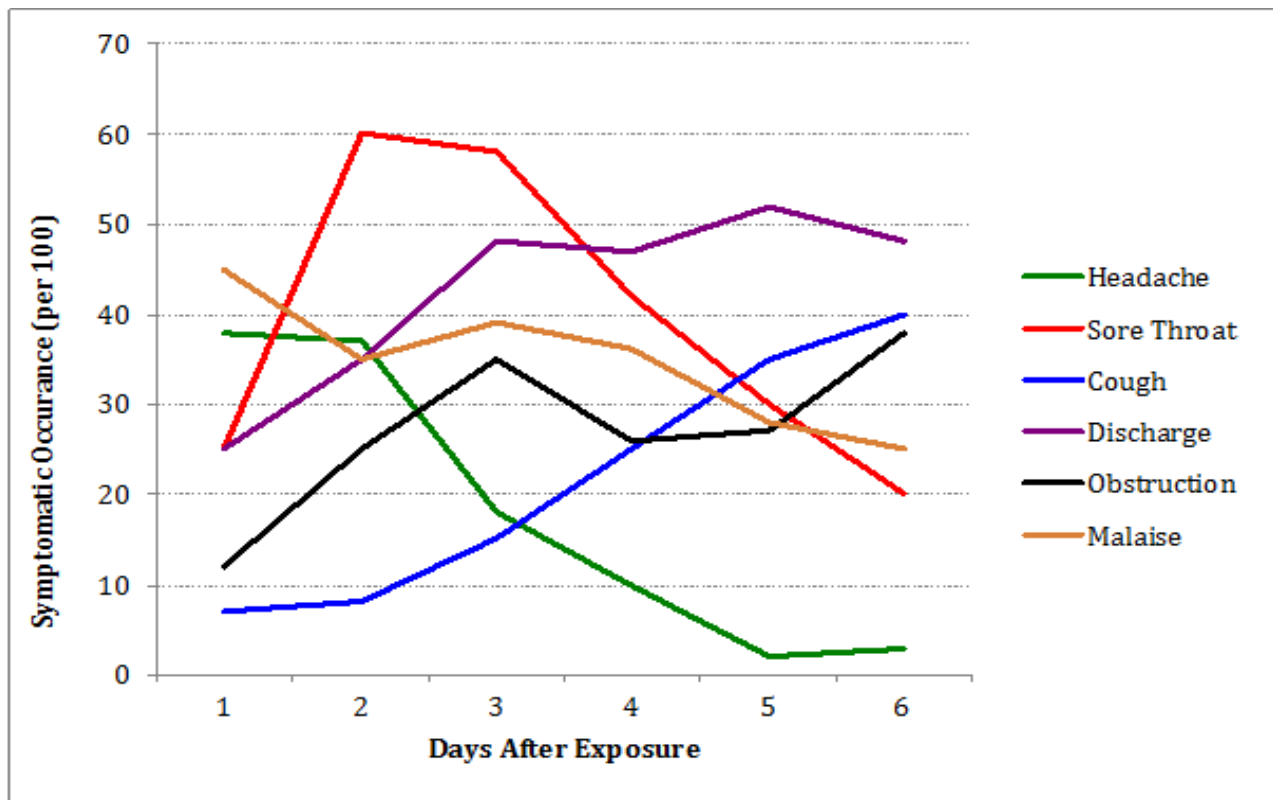


Figure 3. Clinical Symptoms of the Cold Tend to Change over the Course of the Illness

The symptoms of the cold tend to present and resolve in a predictable pattern. Often an ill-defined headache and malaise are the first symptoms patients notice. Most patients experience a sore throat by day 2 post-exposure. This gives way to nasal discharge and nasal obstruction. A cough is usually the last symptom to appear and often persists past the resolution of the other symptoms to around day 7 to 10 post-exposure (data not shown; Heikkinen and Jarvinen, 2003). Diagnostically this information has limited utility because the exact clinical course differs for every patient (Kirkpatrick, 1996). Results adapted from Jackson et al. (1958).

cold-associated viruses on a clinical basis alone is not possible (Nicholson et al., 1997; Arruda et al., 1997; Kirkpatrick, 1996).

Pathogenesis

Role of the Immune Response

The rhinoviruses do not directly cause observable damage to host tissue (Winther et al., 1984a, 1986). The only observable change under histology is an increased number of polymorphonuclear leukocytes in the nasal mucosa following infection (Winther et al., 1984b). Because epithelial cells are left unscathed, it is believed that cold symptoms are caused completely or to a significant extent by an immune response and are not a direct result of viral pathogenesis (Hendley, 1999). The immune response, mediated by signaling molecules released directly or indirectly from infected epithelial cells, results in bradykinin release, which is associated with increased vascular permeability of the venous sinuses, thereby causing the cold's hallmark symptoms of nasal discharge and congestion (Proud et al., 1990). Applying bradykinin in the noses of healthy volunteers

mimics these symptoms of the cold (Proud et al., 1988) and occurs in a dose-dependent fashion (Doyle et al., 1990). A handful of other pro-inflammatory cytokines and chemokines explain the other common cold symptoms such as sneezing, headache, fever, and malaise (Kirchberger et al., 2007). The culpability of the immune response in causing the common cold symptoms have earned it the nickname the, "cytokine disease" (Kirchberger et al., 2007).

Because the inflammatory response to the cold causes infected epithelial cells to undergo apoptosis and subsequent extrusion, it has been proposed that the immune response limits local viral spread (Winther, 2011). Hence, a therapeutic intervention that restricts the immune response for the purposes of symptom suppression may theoretically exacerbate an infection or prolong viral shedding (<http://www.uptodate.com/contents/epidemiology-clinical-manifestations-and-pathogenesis-of-rhinovirus-infections>). However, this remains incompletely understood—for unknown reasons, application of nitric oxide both tapers the immune response to a cold and results in faster rhinovirus clearance (Proud, 2005). This

is an area of research that may yield new therapeutic targets for common cold treatment.

The Cold in Immunocompromised Patients

Studies of the common cold among patients with impaired immune systems allude to the complexity of the immune system's role in rhinovirus infection. In one study of 22 severely myelosuppressed, immunocompromised adults who contracted rhinovirus, 33% of the patients developed a fatal pneumonia at an average of 12 days after the onset of cold symptoms (Ghosh et al., 1999). A more recent study found similar rates of rhinovirus pneumonia among immunosuppressed patients (Jacobs et al., 2013). While 60% of these patients also had a bacterial, viral or fungal co-infection, rhinovirus was the sole detectable pathogen in 40% of the patients with pneumonia (Jacobs et al., 2013). In a study of the first 100 days after hematopoietic cell transplantation, immunosuppressed patients did become symptomatic following rhinovirus or coronavirus infection (Milano et al., 2010). Of these, around 15% of patients continued to shed virus for 3 months or more, but 13% of patients had detectable viral particles and never reported developing clinical symptoms. Another small prospective surveillance study following hematopoietic cell transplantation found that pediatric patients with a rhinovirus infection were more likely to remain asymptomatic and shed viral particles then develop clinical symptoms (Srinivasan et al., 2013). Two patients in this study asymptotically shed rhinovirus for 14 and 34 days before developing symptoms. Another study found that among immunosuppressed adult lung transplant recipients, higher rhinovirus titer was associated with clinical symptoms of the cold, while patients with lower viral loads had clinical symptoms far less frequently (Gerna et al., 2009).

There are limited data on common cold infections among immunocompromised individuals, but the available studies demonstrate that an intact immune system is required to minimize the risk of morbidity and mortality from the cold. Interestingly, immunocompromised patients can still show the signs and symptoms characteristic of an immune response to a cold infection. These patients may not be any more likely to remain asymptomatic than healthy adults with active rhinovirus infections (Gwaltney and Hayden, 1992; Peltola et al., 2008), but in some immunocompromised individuals there is a prolonged latent asymptomatic phase before the patients mount an immune response. It can also take months for these patients to successfully extinguish a cold infection.

Transmission

Hand Contact and Fomites

The classic means by which the cold is transmitted is self-inoculation from a healthy individual's own fingertips (Hendley et al., 1973). Usually a person will contaminate his or her fingers and spread the virus by touching his or her own eyes or nose, which gives the virus access to the nasal mucosa (see "Causes" above). Cold viruses find their way onto hands from either direct contact with someone actively shedding the virus—such as a handshake—or indirectly from contact with an infected environmental surface. A study using PCR in hotel rooms found that ill individuals shed viral particles on 33%–60% of commonly touched fomites like door handles, TV remotes, and light switches (Winther et al., 2007). Rhinoviruses can survive on environmental surfaces for several hours (Gwaltney et al., 1982). Even though viral titer drops by an order of magnitude when a droplet containing active virus dries out, viral traces that are undetectable via tissue culture can still cause an infection (Winther, 2011).

One study in a pediatric ward found that wearing plastic goggles that covered the eyes and nose when holding infants with an ARI decreased infections by 43% among infants and 34% among healthcare workers (Gala et al., 1986). Another study found that 0 of 14 adult participants seated near but physically separated from infants with RSVs became ill, 4 of 10 adults who touched the infants became ill, and 5 of 7 adults who held and played with the infants fell ill (Hall et al., 1981). These results reinforce the conclusion that when caring for someone with the cold, preventing self-inoculation from hand-eye or hand-nose contact is essential for avoiding infection of oneself and others.

Saliva

Saliva is a poor conduit for viral transmission—90% of people with a cold have undetectable levels of virus in their mouth (Kirkpatrick, 1996). Infection that results from kissing a person with the cold is considered a rare occurrence, likely because of the low titer of virus in saliva and because inoculation of pharyngeal mucosa rarely causes infection (Hendley et al., 1973; D'Alessio et al., 1976).

Aerosolized Droplets

Infections caused by aerosolized droplets have been documented, but this is not considered a significant route of transmission (Winther, 2011). Many studies have demonstrated that touching a person with the cold leads to infection far more frequently than physical proximity to a sick individual alone. It has been proposed that perhaps the recirculation of air may increase the chances of cold transmission by raising the

risk of exposure to aerosolized droplets. To test this hypothesis, researchers compared the incidence of colds 1-week post-airplane flight for 1,100 travelers. Half the passengers flew on planes that recirculated cabin air and the other half flew on planes with fresh air ventilation. The researchers found the recirculation of air in the context of commercial flights had no significant effect on cold transmission (Zitter et al., 2002). However, it should be noted that this finding is at odds with data from military barracks, where living in a closed-ventilation barracks was found to raise the relative risk of catching a ARI by 1.5 (95% CI 1.46 - 1.56) (Brundage et al., 1988).

Viral Shedding and Contagiousness

Viral shedding peaks 48–72 hr after infection (Hendley and Gwaltney, 2004). In one study, 24 married couples were monitored after a spouse was inoculated with rhinovirus. The researchers found that the risk factors for successful pathogen transmission were high viral load, moderate symptoms, and time spent with spouse (D'Alessio et al., 1976). This finding indicated that viral spread depends on peak viral load coinciding with the presence of only mild symptoms. Hence, most transmissions of the cold tend to occur within the first 5 days after exposure. Even though symptoms usually taper off after 5–7 days, viral shedding continues for up to 2 weeks after infection, meaning a recently ill person can still unknowingly spread the cold (Winther et al., 1986).

Prevention

Vaccination

Several distinct families of viruses cause the cold (Monto and Sullivan, 1993). Even among the most common cause of the cold, the rhinovirus, there are over 100 virus serotypes, thus far thwarting vaccination efforts (Heikkinen and Jarvinen, 2003). Targeted therapies might still be possible, since many pathogeneses share common pathways. For example, upregulating a decoy form of ICAM-1—the surface protein that 90% of rhinoviruses use to gain entry into epithelial cells—decreases rhinovirus infectivity in vitro (Whiteman et al., 2003). The recent discovery of conserved motifs among broad serotypes of rhinovirus may also potentially yield targets for drug development (Poland and Barry, 2009; Palmenberg et al., 2009). Non-vaccine strategies have been the primary area of research in cold prevention research.

Pharmaceutical Prophylaxis

Importation into a household by school-aged children is a common route of cold transmission to adults (Monto and Sullivan, 1993). Hence, one preventative strategy is to take aggressive measures that stop the infection of

family members when one member of a household catches the cold.

Prophylactic pharmaceutical agents demonstrated to prevent cold infections exist, but these still carry unpalatable side effects. For example in one study, whenever a participant developed a cold, his or her family would begin a 7-day prophylactic course of intranasal interferon (Douglas et al., 1986). The treatment reduced ARI illnesses among family members by 41%, but each course of treatment had around a 12% risk of intranasal bleeding. Intranasal interferon was particularly efficacious for rhinovirus infections, decreasing infections by 86%. However, it is not possible to clinically determine if a cold is caused by rhinovirus as opposed to another viral pathogen, limiting the utility of the observed efficacy (Nicholson et al., 1997; Arruda et al., 1997; Kirkpatrick, 1996). Additionally, interferon use led to a concerning leukocyte accumulation in the mucosa (Hayden et al., 1987). Other antiviral chemotherapies (e.g., ICAM-1 blocker, capsid binding agents, and protease inhibitors) have similarly failed to show a promising risk to benefit ratio (Winther, 2011).

Weather and Isolation

Contrary to popular belief, there is no demonstrated association between being in cold weather and common cold susceptibility. Newcomers and long-time workers at a remote research base in Antarctica were found to be equally susceptible to catching the cold (Warshauer et al., 1989). While a medical school class' isolation might seem protective, another Antarctica study of ARI's during a period of absolute isolation found that a respiratory infection present at the beginning of isolation persisted throughout the 6 months of winter isolation (Flynn et al., 1977).

Vitamin C

Another popular means of cold prevention, vitamin C supplementation, was examined in a meta-analysis of 29 trials (Hemila and Chalker, 2013). Together the studies include 10,708 participants from the general public and show vitamin C supplementation does not decrease common cold incidence, either when taken regularly or in large prophylactic doses (RR 0.97, 95% CI 0.94 to 1.00) (Hemila and Chalker, 2013). Because vitamin C does not reduce cold incidence in the general public, the authors suggested that routine vitamin C supplementation "is not justified." While regular supplementation of vitamin C was associated with an 8% reduction of symptom duration in adults and 14% reduction in children, given the wide variation of cold presentations (Monto and Sullivan, 1993), it is possible that this statistical finding is entirely sub-clinical and is not relevant for a population-wide recommendation. Additionally, it was found that mega-doses of vitamin C

after the onset of clinical symptoms had no effect on illness duration or symptom intensity.

Curiously, five studies of 598 extreme athletes under conditions of intense but brief physical stress—individuals at a ski camp (Ritzel, 1961), runners in an ultra-marathon (Peters et al., 1993), etc.—receive a clear and consistently positive benefit from vitamin C supplementation (Hemila and Chalker, 2013). For example, in one study half of the Canadian military recruits taking part in arctic training exercises were given a daily placebo and the other half were given daily vitamin C (Sabiston and Radomski, 1974). To minimize bias, the supplemented group was only revealed to both participants and researchers at the end of the study through the measurement of intravenous ascorbate levels. Among 112 men, 25% taking the placebo and only 10% receiving vitamin C caught the cold. The five studies show that vitamin C supplementation under conditions of acute physical stress cuts the incidence of cold infections by half (RR 0.48, 95% CI 0.35 to 0.64) (Hemila and Chalker, 2013). Two other randomized controlled trials found that individuals under conditions of prolonged physical stress—marine recruits at boot camp and competitive adolescent swimmers—received no benefit from vitamin C in terms of cold prevention (Pitt and Costrini, 1979; Constantini et al., 2011). This perhaps indicates that the supplementation with vitamin C has a substantial benefit, but only under conditions of acute physical stress (Hemila and Chalker, 2013).

Hence, aside for a narrow subset of extreme athletes, vitamin C has no demonstrated therapeutic benefit. Yet, even if it will not help treat or prevent the cold, especially given the low risk and cost of vitamin C, supplementation does not hurt.

Surgical Masks

While masks can prevent cold transmission in hospital wards—especially when they prevent self-inoculation by covering the eyes and nose (Gala et al., 1986)—surgical masks have not yet been demonstrated to be effective in more general contexts. One prospective study found that wearing a surgical mask has no effect on likelihood of catching a cold, but it did significantly make a mask-wearing participant more likely to experience headaches (Jacobs et al., 2009). Yet it is worth noting that this 77-day study with 32 participants was underpowered and would only have detected an absolute risk reduction of 60% from wearing a mask. Unfortunately, other

drastic or novel approaches have not yet shown great promise either (Jefferson et al., 2011). For example, use of tissue paper with virucidal properties did not effectively reduce the frequency of colds (Farr et al., 1988).

Social Networks

Contemporary studies into the social component of disease transmission have utilized quirky features of social networks to successfully prevent the spread of infectious diseases and computer viruses. For example, the targeted vaccination of “central” individuals who have the most connections in a social network can raise population immunity (Pastor-Satorras and Vespignani, 2002; Cohen et al., 2003). Because central individuals have more connections in a social network, they are likely to spread a disease to more people and become infected earlier in an outbreak. Another feature of social networks is the so-called “friendship paradox,” which is the observation that your friends have more friends than you do—or that your friends are likely more central than you are. Researchers used this during a flu outbreak at Harvard College and found that if random volunteers nominated a friend, because that friend was more likely to be a central individual—and hence more likely to get sick earlier in an outbreak—monitoring the nominated, central friends for signs of the flu significantly improved early flu detection (Figure 4) (Christakis and Fowler, 2010). At this time, however, a study utilizing social

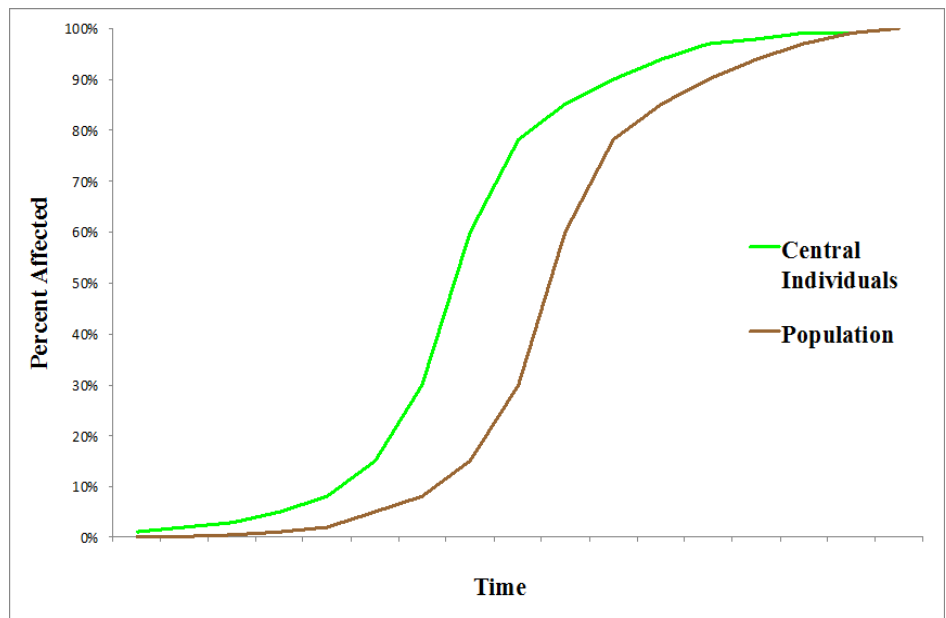


Figure 4. Early Infection of Central Individuals in an Outbreak

Your friends tend to be more centrally located in social networks than you are. Hence in the conditions of social spreading, “central” individuals in a social network pick up infections earlier than random individuals. Researchers were able to use this feature of social networks in real-time to detect an influenza outbreak significantly earlier than traditional surveillance methods (Christakis and Fowler, 2010). Theoretical results adapted from Christakis and Fowler (2010).

network structure for early detection or prevention has not been attempted for the common cold.

Hand Washing—The Punch Line

What do we have to prevent the cold, then? The answer can be gleaned from a classic experiment in 1980 in which one group of random volunteers dipped their fingers in dilute iodine solution—it was known to have virucidal properties (Hendley et al., 1978)—and were compared to volunteers who dipped their hands into water that was died to look and smell like iodine (Gwaltney et al., 1980). Immediately after drying their hands, volunteers made hand contact with rhinovirus-positive donors who had just picked their noses (“The donors contaminated their hands with nasal secretions by finger-to-nose contact”), and 15 min later, volunteers touched their own eyes and noses. This was repeated for 3 days. None of the eight iodine-exposed volunteers became infected, while all seven controls became ill ($p < 0.001$). Unfortunately, routine iodine use is impractical given that many patients do like having iodine-stained hands.

Subsequent randomized controlled trials demonstrated that good hand hygiene leads to a 20% decrease in cold incidence (Carabin et al., 1999; Ladegaard and Stage, 1999). One crossover study found that giving children hand-sanitizer to compliment normal hand washing resulted in a 50% decline in ARI incidence (Dyer et al., 2000). A meta-analysis of 67 studies on preventing ARI transmission concurred hygienic measures are the most effective measure to prevent ARI infection (Jefferson et al., 2011).

Conclusion

As discussed throughout this review, many of the most illustrative studies of the common cold rely on despotic study protocols. Some studies leveraged drastic geographical conditions—at Antarctic research bases and military exercises on the Northern frontier—to study the cold in isolation (Warshauer et al., 1989; Flynn et al., 1977; Sabiston and Radomski, 1974). Other researchers intentionally infected healthy volunteers with the cold, ranging from the infection of married people to study risk factors associated with transmission (D’Alessio et al., 1976) to infecting COPD patients simply to prove that the cold causes COPD exacerbation (Mallia et al., 2011). Such measures were not utilized for the purposes of the brief case study of the outbreak at Harvard Medical School. Good-hearted volunteers and the self-limited nature of the cold have made it possible for researchers to illuminate the pathogenesis, transmissions, and prevention of mankind’s most common ailment.

The case study from Harvard Medical School revealed two risk factors significantly associated with contracting

an ARI. However, the gross social patterns of behavior elucidated in the study did not capture unique social interactions with the granularity needed to prospectively predict the spread of disease or retrospectively describe the specific social interactions that tended to promote disease transmission. Disease transmission in social networks is an unexplored area of research in common cold transmission, and the methods discussed above have implications for preventing and detecting outbreaks among small semi-isolated communities such as universities, hospital wards, military bases, and retirement communities. Such prevention efforts are especially important given that in this outbreak ill students each infected 3.5 of their colleagues.

Thus far, good hand hygiene is the best method of preventing common cold transmission, especially when around children (Jefferson et al., 2011). A survey of the literature supports this intuitive conclusion—self-inoculation from one’s fingers through the eyes or nose is the most frequent means by which the cold is transmitted (Hendley et al., 1973). Saliva and aerosolized droplets rarely cause infections (Winther, 2011; Kirkpatrick, 1996; D’Alessio et al., 1976). Yet infectious viral particles can persist on hands and commonly used fomites for hours (Winther et al., 2007; Gwaltney et al., 1982). Peak viral shedding coincides with early cold symptoms such as rhinorrhea (Jackson et al., 1958; Hendley and Gwaltney, 2004). Cold symptoms are completely attributable to our immune response (Hendley, 1999). Children tend to have more colds per year than adults (Pappas et al., 2008) and are frequently responsible for exposing family members to the numerous cold pathogens (Monto and Sullivan, 1993). Annually, the cold accrues more direct medical costs than influenza and is the number one reason for missed work and school (Fendrick et al., 2003; Molinari et al., 2007). There are no effective treatments for the cold (<http://www.uptodate.com/contents/the-common-cold-in-adults-treatment-and-prevention>). This makes prevention especially important for vulnerable populations such as asthmatic, COPD, elderly, and immunocompromised patients (Nicholson et al., 1996; Mallia et al., 2011; Teichtahl et al., 1997; Ghosh et al., 1999). Alas, as a prevention strategy, hand washing is almost disappointingly simple. But given hand washing’s safety (consider nose bleeds from intranasal interferon) (Douglas et al., 1986; Hayden et al., 1987), ease (consider surgical masks in public) (Jacobs et al., 2009), and efficacy (consider vitamin C) (Hemila and Chalker, 2013), perhaps a simple solution is not a bad thing for such a common problem.

Acknowledgments

The author would like to thank Annie Morgan for essential help with data analysis for the case study at Harvard Medical School, and extends aHi nother warm thank you to the HMSR staff for their patience with this

manuscript. The author has no conflicts of interest to disclose.

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Article

The Management of Stasis Dermatitis and Chronic Venous Insufficiency in Patients Refractory to Conservative Therapies

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Synopsis: Chronic venous insufficiency (CVI) is a common problem in primary care clinics, characterized by poorly functioning veins, leading to edema, skin changes, and even ulceration of the affected limb. Though conservative measures are often helpful, many patients ultimately require further intervention.

Case

A 76-year-old woman with a lengthy smoking history has been managed conservatively over the last year for her lower extremity chronic venous insufficiency (CVI) with only modest symptomatic improvements. Many conservative therapies have been trialed, including compression, elevation, aerobic exercise, aspirin, as well as topical emollients and corticosteroids, all without resolution of her disease. Given her persistent stasis dermatitis and chronic swelling, she expresses an interest in pursuing a surgical intervention for her venous insufficiency but is concerned about complications such as deep vein thrombosis (DVT). The following review will address next steps in management for CVI in a 76-year-old woman with an inadequate response to conservative medical therapy.

Background

Lower extremity venous disease is a common problem in both primary care and specialist practices with wide ranging clinical consequences. In some studies, the prevalence of this disorder has been found to be nearly 50%, though variations exist depending on the population studied (Zahariev et al., 2009). Clinical consequences range from benign cosmetic changes to painful skin breakdown that predisposes patients to a great deal of morbidity from secondary infection, all with a significant impact on a patient's quality of life (Tsai et al., 2005). Fortunately, there have been highly effective treatments developed for the management of this disease. Because the underlying pathogenesis of venous disease is due to incompetent veins that then swell and cause edema and inflammation, the goal of all of the treatments described below is to sclerose the

dysfunctional veins and prevent blood from pooling in them.

The patient described above carried a clinical diagnosis at the time of evaluation of CVI, which, according to nomenclature set forth by a 2009 article clarifying the terminology of lower extremity venous disorders, constitutes functional abnormalities of the venous system along with advanced signs and symptoms of disease, including moderate or severe edema, skin changes, or venous ulcers (Eklöf et al., 2009). Though the patient lacked lower extremity ulcerations, her skin exam demonstrated evidence of significant stasis dermatitis and edema (Figure 1), while an ultrasound examination showed she had abnormal retrograde flow in her great saphenous Vein (GSV), confirming an anatomical basis to her CVI. Thus, by a widely used scoring criteria known as Clinical-Etiology-Anatomy-Pathophysiology (CEAP) (Table 1) classification, the patient was category C_{4b}-E_p-A_s-P_r (Eklöf et al., 2004). Though there are currently no official guidelines published by vascular societies in the US for the management of CVI, review articles published in *Circulation* in 2005 and in the *New England Journal of Medicine* in 2009 recommend CVI be managed medically initially, using measures such as leg elevation, exercise, and compression therapy along with wound care to keep the overlying skin moisturized (Raju and Neglén 2009; Eberhardt and Raffetto 2005). For patients with an unsatisfactory response or with advanced disease (CEAP 3-6), interventions may be warranted. Our patient had been managed using such therapies for a duration of several months.



Figure 1. Ulcerated Lower Extremity Lesion

Classic appearance of advanced stasis dermatitis secondary to CVI, leading to central ulceration and necrosis. Note the characteristic presence hyperpigmentation of the overlying skin, ulceration, necrosis, and diffuse edema. Taken from CDC Public Health Image Library, Kraus 1981.

Should a patient be deemed clinically appropriate for intervention following a trial of conservative management, the interventional options are divided broadly into minimally invasive ablative therapy using either chemical (ultrasound-guided foam sclerotherapy [UGFS]), thermal (endovenous laser ablation [EVLA], endovenous steam ablation [EVSA], or radiofrequency ablation [RFA]), or mechanical (vein stripping or ligation). There are also three surgical techniques that aim to occlude perforator veins, repair an iliac vein obstruction, or reconstruct deep valves. However, these three latter surgical therapies are meant for patients in whom either the anatomical disturbance is in the perforator veins, have an obstruction in the iliac vein, or have failed other simpler therapy, respectively (Raju and Neglén 2009). Our patient has not met any of these criteria and thus is primarily a candidate for treatment by one of the four ablative techniques. However, in patients who are healthy enough for surgery and meet these criteria, a surgical approach might have been considered. A recent review article, however, demonstrated that endovenous approaches are at least as effective as surgical ones (Nesbitt et al., 2014).

Table 1. Breakdown of CEAP Classification System

Clinical	
C ₀	No clinical signs of disease
C ₁	Telangiectasia and reticular veins
C ₂	Tortuous varicose veins
C ₃	Edema
C _{4A}	Stasis dermatitis
C _{4B}	Lipodermatosclerosis
C ₅	Skin changes with past ulceration
C ₆	Skin changes with active ulceration
Etiological	
E _C	Congenital
E _P	Primary (most cases)
E _S	Secondary (to thrombosis, trauma)
E _N	Not identified
Anatomic	
A _S	Superficial veins
A _P	Perforator veins
A _D	Deep veins
A _N	Not identified
Pathophysiological	
P _R	Reflux
P _O	Obstruction
P _{R,O}	Reflux and obstruction
P _N	Not identified

Each category corresponds to a clinically determined score defining the disease severity, etiology, anatomic location, or underlying cause of the CVI. The goal of treatment is to modify and prevent disease progression through categories. Each limb may be further characterized as symptomatic or asymptomatic. Data from Eklof et al., 2004. Table modified from UpToDate, *Classification of Lower Extremity Chronic Venous Disorders*.

Table 2. Comparison of Percentage of Successful Outcomes at 3 Mo. and 5 Yr. by Ablation Method

	3 Months	5 Years
Stripping or ligation	80.4% (72.3%–86.5%)	75.7% (67.9%–82.1%)
UGFS	82.1% (72.5%–88.9%)	73.5% (62.8%–82.1%)
RFA	88.8% (83.6%–92.5%)	79.9% (59.5%–91.5%)
EVLA	92.9% (90.2%–94.8%)	95.4% (79.7%–99.1%)

These results show the highest rate of successful outcomes as assessed by ultrasound are seen with EVLA, both at 3 months and at 5 years. The 95% CI is given in parentheses. UGFS: ultrasound-guided foam sclerotherapy; RFA: radio frequency ablation; EVLA: endovenous laser ablation. Data is extracted from van den Bos et al. (2009).

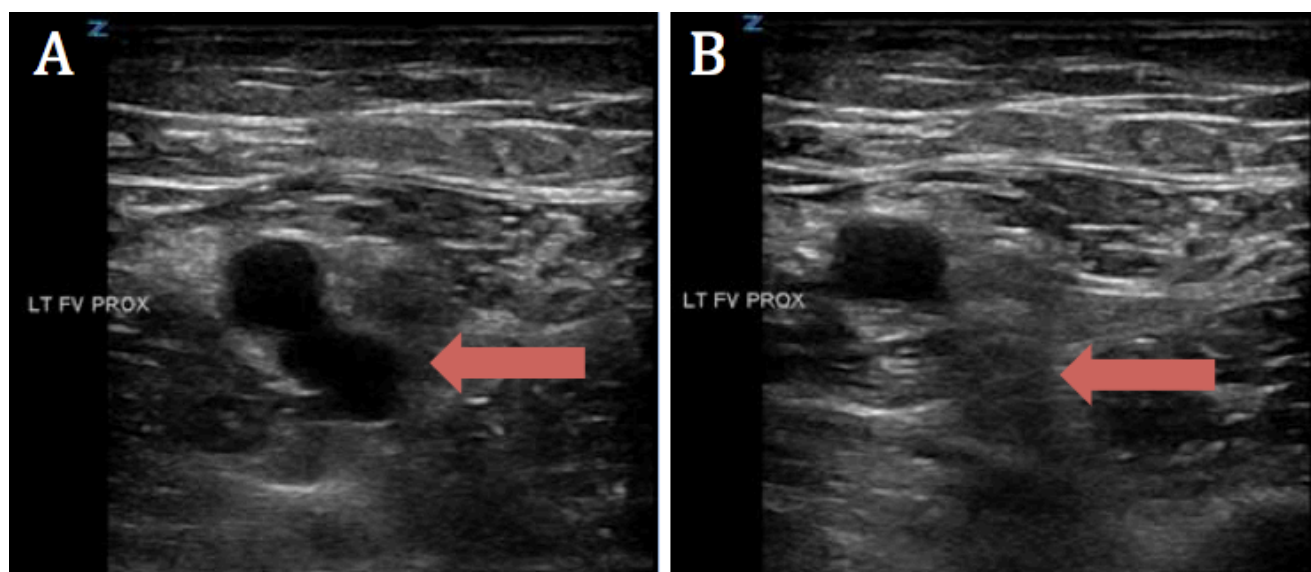


Figure 2. Normal Compressibility of the Popliteal Vein as Assessed by Ultrasound

The image on the left (A) shows the proximal portion of the left femoral artery (superior) and vein (inferior, red arrow), and the image on the right (B) shows the same femoral artery and vein under compression. Because of the relatively low intraluminal pressure in the vein, it is compressible and occluded and therefore disappears from ultrasound. If the vein were found not to be compressible, it would be suggestive of a thrombus within the lumen. When this occurs in the deep veins of an extremity, it is known as a DVT. CVI is not usually caused by DVT.

Review

There are two seminal studies in the literature that seek to compare the efficacy of the ablational methods for which our patient is a candidate. *Endovenous Therapies Of Lower Extremity Varicosities: A Meta-Analysis* was published in 2008 and investigated 119 retrieved studies, of which the authors ultimately included 64 that assessed a total of 12,320 limbs. They included any randomized controlled trial (RCT), clinical trials, or case series of human lower extremity varicosities treated by EVLA, UGFS, RFA, or surgical stripping/ligation and that used post-procedural ultrasound to determine whether the intervention was successful. After a mean follow-up period of 32.2 months, the authors compared the success rates at different time points up to 5 years to assess the percent of successful outcomes (summarized below and in Table 2). It was found that for surgical stripping or ligation was 80.4% successful at 3 months and 75.7% successful at 5 years. The rate of success increased incrementally between UGFS, then RFA, and appears to be highest for EVLA with a 92.9% and 95.4% at 3 months and 5 years, respectively. When the results were compared, the higher success rate of EVLA was statistically significant ($p < 0.05$) (van den Bos et al., 2009).

These results established for the first time in a large study the suggestion that EVLA is superior in achieving a successful outcome as measured by ultrasound compared with other methods. However, while this ameta-analysis successfully summarizes much of the existing evidence and directly compares the different

methods, it also has several limitations. The study participants, like our patient, are limited to patients under treatment for venous reflux of either the GSV or SSV. However, our patient is CEAP 4b, and there is no mention of the patient characteristics in this study, particularly with regard to their CEAP score, making it difficult to apply these results to particular patient groups. Further, this study limits its outcome measures to the ultrasound occlusion of the vein (Figure 2). While this is the gold standard in the field for determining a successful intervention, it will not necessarily correlate with improvement in a patient's symptoms. The authors point this out, noting that the correlation with scores such as the Health-Related Quality of Life and complication rates should be considered particularly when multiple interventions are highly effective (such as for instance HVLA and RFA) in distinguishing between them. In addition, when interventions are comparatively effective, cost analysis is also warranted to guide recommendations on a national level.

Fortunately, there is a recently published RCT comparing EVLA, UGFS, and ligation/stripping by Biemans et al., (2013). This study was conducted between 2009 and 2010 in the Netherlands, and it enrolled 240 consecutive patient legs (223 patients) during this study period. The patients had to have ultrasonographic evidence of GSV reflux that was reported to be symptomatic. It randomized these eligible patients to one of the three treatment arms (either EVLA, UGFS, or ligation stripping). Over the course of the 1 year of follow-up in this study, the primary

outcome measure was again the rate of anatomic success on follow-up ultrasound. However, this study was comprehensive in that it also tracked changes in CEAP score, the frequency and nature of complications, and subjective quality of life improvements in patients as secondary outcomes. Primary outcome results showed a high success rate by ultrasound, demonstrating total occlusion in 88.5% of EVLA patients, 88.2% in the stripping/ligation group, and 72.7% of the UGFS group, which was lower than the EVLA and stripping/ligation group ($p < 0.02$) (Biemans et al., 2013). Notably, 10% of the stripping/ligation group demonstrated neovascularization at 1 year, an undesirable consequence that may compromise the long-term success of the procedure. All three groups were found to have significant improvement of their CEAP score; however, none of these changes were statistically significant ($p < 0.05$) between any of the groups. Similarly, while quality-of-life scores improved in all three groups, no statistically significant differences were found between any of the groups. Complication rates were low overall, with 7, 5, and 11 patients experiencing post-operative complications in the EVLA, UGFS, and stripping/ligation groups, respectively (Table 2). The stripping/ligation group specifically had a significantly higher rate of wound infections ($p = 0.03$). Superficial vein thrombosis accounted for 10 of the 23 total complications. Notably, there were no DVTs reported.

EVSA is the newest ablation technique, and the LAST trial (van den Bos et al., 2014) is the only major studying the efficacy of this new therapy. Because of previous findings suggesting the high success rate of EVLA, they compared EVSA only to EVLA by enrolling 227 legs and observing them for 1 year. Primary outcomes were vein ablation at 1 year and a validated measure of CVI severity (venous clinical severity score [VCSS]). Secondary outcomes were pain, satisfaction, duration of analgesia use, complication rates, and others. From an efficacy standpoint, EVSA was shown to be non-inferior to EVLA, and many of the secondary outcomes were in favor of EVSA (though notably, complication rates were comparable) (van den Bos et al., 2014), though this is the highest quality evidence currently available, there are again several potential limitations in using the data to recommend EVLA or EVSA to patients. In the Biemans et al., (2013) trial, EVLA patients are significantly younger than either the UGFS or stripping/ligation, which may falsely introduce healthier patients into this cohort. Another major shortcoming of both studies is that there is only 1 year of follow-up, which is significant considering that previous studies have suggested the surgical techniques do not have equivalent long-term success rates. The studies also have only a small number of total complications, which may suggest it is not powered to detect differences between the rate of complications between these methods. This is important given the theoretical risk of very clinically

important complications such as DVT. Finally, despite the promise of EVSA, it is a new technique that has not been studied in the long-term, and not all clinicians may be comfortable adopting it immediately.

Complication Rates

Given the above studies, it would seem EVLA or EVSA is a suitable option for patients, given its high success rate and improvement in CEAP and quality of life scores, which are at least comparable to stripping/ligation and UGFS. However, the question of the risk of complications in these patients, specifically DVT, remains largely unanswered. For this, there are several studies devoted to this question. First, a Mayo Clinic study enrolled 130 limbs in 92 patients in a non-randomized protocol. Of the 130 limbs, 124 were CEAP 2-4. DVT was assessed for in 70% of the EVLA group by ultrasound, with the finding of three thrombi (2.4% of cohort) in the common femoral vein (CFV), one requiring IVC filter placement, all of which were treated with heparin and were without further complication such as extension of the clot or pulmonary embolus (Puggioni et al., 2005). There was no significant difference between the overall rate of complications between EVLA and RFA in this study. In another larger retrospective study published this year comparing RFA and EVLA, both EVLA and RFA again demonstrated low (<1%) rates of DVT and no significant differences in the rate of complications between the two therapies (Marsh et al., 2010). One case of pulmonary embolus was reported in the RFA group. In addition, two new studies from UC Davis and Rush Medical Center suggested that age >66, female gender, and tobacco use were all associated with increased post-procedure DVT risk, perhaps suggesting some patient's risk is higher than even those in the earlier cited studies (Chi and Woods, 2013; Jacobs et al., 2013).

Conclusions

In consulting the literature in search of a therapeutic recommendation for CVI, it is apparent the treatment options are rapidly evolving as new technologies emerge. The first RCT comparing the new minimally invasive techniques gave preliminary evidence that EVLA and EVSA have among the highest rates of success in terms of correcting the underlying anatomical abnormalities of CVI while maintaining at least equivalent rates of subjective improvement with other therapies. In preliminary studies, EVSA has had a high success rate while simultaneously decreasing pain and analgesic use and improving patient satisfaction. These findings should be interpreted with caution until they have been duplicated in larger patient cohorts over more extended periods of time, and this research is of particular importance moving forward. Additional studies cited above have demonstrated a low rate of complications and

DVTs in EVLA patients, with the caveat that the study populations in the available literature may not reflect a given patient's comorbidities, CEAP score, or age.

Besides ablatational therapies, the other alternative for patients to consider is ongoing medical management, in consideration of the fact that even a low risk of complications may not be acceptable in an otherwise frail patient for whom a DVT leading to a pulmonary embolus could be fatal. Conversely, equally threatening are the complications and debilitating symptoms from further progression of her CVI that include ulceration and secondary infection, or immobilization leading to DVT. Perhaps the next area of endeavor in CVI will be in preventing the venous anomalies from developing years prior to the onset of symptomatic CVI.

The management of CVI patients was previously challenging given the lack of data or therapeutic options. However, for patients who have had an insufficient response to medical therapy and/or clinically severe disease, there are now several interventional options available. Following a thorough review of this data, the patient described earlier was referred for consultation with a vascular surgeon, who concurred with the findings above and recommended EVLA as the best therapeutic option and one with among the lowest risk profile, which was deemed clinically acceptable in our patient. Therefore, this patient underwent an uncomplicated EVLA procedure and has since seen significant clinical and symptomatic improvement in her lower extremity venous disease as a result.

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Article

Preparing a New Generation of Clinicians for the Era of Big Data

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Synopsis: As medicine becomes increasingly complex and financially constrained, it will be the responsibility of every clinician to understand and participate in the enterprise of extracting lessons learned from digitally captured patient care.

Introduction

In the past, both outpatient and inpatient clinical data were entered and stored in paper formats that were not systematically organized, were accessible only at a single physical place at a time, and were stored—when not lost—in distant, variably efficient medical records departments. With the current, widespread adoption of Electronic Health Records (EHRs), such data should now be made available and leveraged to generate knowledge. But even post-digitization, the information generated from everyday patient encounters remains under-utilized. Our ability and capacity to train both new and experienced clinicians to manage this tremendous amount of data lag far behind the pace of the data revolution. Medical education at all levels must come to address data management and utilization issues as we enter the era of Big Data in the clinical domain.

In this paper, we review the potential that Big Data holds in knowledge discovery in medicine and propose to incorporate more data science into the medical school curriculum. In this context, we present our work with the Multi-parameter Intelligent Monitoring in Intensive Care (MIMIC) database, including the Critical Data marathons that we organize.

The Problem: Data Deserts and Dead Ends

Diagnostic and therapeutic technologies continue to evolve rapidly, and both individual practitioners and clinical teams face increasingly complex decisions. Unfortunately, the current state of medical knowledge does not provide the guidance to make the majority of clinical decisions on the basis of evidence: According to the 2012 Institute of Medicine Committee Report, only 10%–20% of clinical decisions are evidence based. The problem even extends to the creation of clinical practice

guidelines (CPGs). Nearly 50% of recommendations made in specialty society guidelines rely on expert opinion rather than experimental data (Committee on the Learning Health Care System in America, 2012; Kung et al., 2012). Furthermore, the creation process of CPGs is “marred by weak methods and financial conflicts of interest,” rendering current CPGs potentially less trustworthy (Steinbrook, 2014).

The present research infrastructure is inefficient and frequently produces unreliable results that cannot be replicated (Steinbrook, 2014). Even randomized controlled trials (RCTs), the traditional gold standards of the research reliability hierarchy, are not without limitations. They can be costly, labor intensive, and slow and can return results that are seldom generalizable to every patient population. It is impossible for a tightly controlled RCT to capture the full, interactive, and contextual details of the actual issues that arise in real clinics and inpatient units. Furthermore, many pertinent but unresolved clinical and medical systems issues do not seem to have attracted the interest of the research enterprise, which has come to focus instead on cellular and molecular investigations and single-agent (e.g., a drug or device) effects. For clinicians, the end result is a bit of a “data desert” when it comes to making decisions.

Electronic medical record (EMR) data are digitally archived and can subsequently be extracted and analyzed. Between 2011 and 2019, the prevalence of EMRs is expected to grow from 34% to 90% among office-based practices, and the majority of hospitals have replaced or are in the process of replacing paper systems with comprehensive, enterprise EMRs (Committee on the Learning Health Care System in America; Hsiao et al., 2011; Macleod et al., 2014). The power of scale

intrinsic to this digital transformation opens the door to a massive amount of currently untapped information. The data, if properly analyzed and meaningfully interpreted, could vastly improve our conception and development of best practices. The possibilities for quality improvement, increased safety, process optimization, and personalization of clinical decisions range from impressive to revolutionary. The National Institutes of Health (NIH) and other major grant organizations have begun to recognize the power of Big Data in knowledge creation and are offering grants to support investigators in this area (<http://grants.nih.gov/grants/guide/rfa-files/RFA-HG-13-009.html>).

Already, a number of organizations and academic medical centers have begun to harness the potential of Big Data through application in both clinical and research arenas. To cite a few examples, the Mayo Clinic has implemented software that were developed using clinical data, including the Ambient Warning and Response Evaluation (AWARE) system that supports best practice in the ICU and operating room; Syndromic Surveillance, which provides “sniffers” to detect sepsis; and YES Board, a multi-patient management tool that offers real-time situational awareness for the Emergency Department (Milliard, 2014). At Cleveland Clinic, medical calculators have been developed that take into account patient demographics as well as details about the medical condition in order to guide clinicians and patients in decision making with regard to tests and treatments (Landro, 2014). Finally, efforts are underway to build international clinical databases. With funding from the NIH, the Laboratory of Computational Physiology at the Harvard-MIT Division of Health Science and Technology is spearheading an initiative to create an open-access repository of EHR data from ICUs across partner countries, including the US, Belgium, the United Kingdom, and France (Celi et al., 2013). Funded by the European Commission, the Brain Monitoring with Information Technology (BrainIT) group has created a core data set collected from 20 neurointensive care centers from 11 countries across Europe (<http://www.brain-it.eu/>).

This digital transformation has taken place before the eyes, but below the radar screen, of the medical education system. While clinical workflow has been irreversibly altered by the implementation of these systems, education and training largely proceed without taking these issues into account. Unfortunately, few physician educators are adequately trained in data management and analysis (Lucey, 2013). Little to no time in training is spent teaching the fundamentals of data science, knowledge creation, and outcomes-based practice. Most medical schools devote a single month to basic epidemiology and statistics (Looney et al., 1998; <https://www.aamc.org/initiatives/medaps/curriculumreports/>). Residency curriculums require physicians-in-training to

utilize a variety of software applications for patient care, but there are few resources dedicated to improve our use of the information we create: the general systems principles involved in the digital transformation of medicine are not being conveyed, perhaps because they are still in the process of being formulated.

The Approach: Leveraging Data to Meet Clinical Needs

Beyond simple user principles, trainees do not learn the skills and concepts necessary for the optimal use of EMRs, including knowledge creation and personalized clinical decision making through analysis of large data sets. To date, this is largely because such systems have not been designed or implemented with these goals in mind. In the coming era of “Big Data,” our community of medical educators and researchers must leverage digital systems for this purpose and find a way to prepare trainees for this critical role. Most current medical educators are not particularly well versed in these issues, which arose after their own training and represent distinctive areas of knowledge lying outside the historical clinical domain. Academic medical informatics departments should be actively enlisted and involved in the response to this challenge. It is likely that medical educators themselves will need to be educated by internal and external experts before they can proceed to educate others. Maximizing knowledge generation from EMRs will require some redefinition of the roles of the contemporary doctor. Many barriers exist to incorporating new courses into already overloaded medical school curricula. A reappraisal is needed to determine what can be omitted or taught more efficiently. As an example, elective rotations in biostatistics and Big Data could be offered to fourth year medical students. The fourth year medical school curriculum is generally less structured than the first three years (Walling and Merando, 2010), and an introduction to secondary use of EHR data may provide a foundation for students to be able to contribute to knowledge discovery regardless of the career path they eventually choose.

In order to support this transformation in clinical practice and research, physicians-in-training will need to be educated to some reasonable degree in the analysis of large data sets in collaboration with data scientists and biostatisticians. The multi-disciplinary team is now expanding beyond nurses, pharmacists, and other traditional allied health personnel and will include individuals with advanced data analytic abilities.

Our group has been working with data scientists from the Massachusetts Institute of Technology (MIT) and biostatisticians from the Harvard School of Public Health using the MIMIC database. This database, which holds clinical data from over 60,000 stays at the intensive care units (ICUs) at Beth Israel Deaconess

Medical Center, has been meticulously de-identified and is freely shared online with the research community (Saeed et al., 2011). It provides a platform from which “crowdsourcing” can be applied in the generation of hypotheses, discovery of knowledge, and evidence creation in the practice of critical care.

MIMIC is a public-access database, and our group actively encourages participation from clinicians at all levels of training, including medical students, residents, fellows, and faculty. Clinicians are partnered with data scientists from the Massachusetts Institute of Technology and the Harvard School of Public Health. The clinician-data scientist team, under the supervision of an expert in the field of clinical informatics, extracts data from MIMIC and performs the necessary analyses to answer questions that arise during rounds.

Current Work and Outcomes

To date, more than 50 clinicians, including doctors, nurses, and pharmacists, have worked alongside data scientists on a wide range of projects. These projects have already begun to answer the kinds of novel clinical questions that would have taken far more time and resources to address in a RCT. Through the use of data extracted from the MIMIC database, many original research articles have already been published, and many more are in the pipeline. The range of topics is broad and includes studies exploring the optimal dosing of medications, the creation of prediction models, and the discovery of previously unknown or underappreciated relationships. To date, over 50 journal articles have been published using data from MIMIC (<https://mimic.physionet.org/about/publications.html>).

Importantly, medical students and resident clinicians frequently maintain their relationship with the data scientists as they progress in their training. The highly accessible and open nature of MIMIC allows for continuation of academic projects even from remote locations. This is producing a cohort of physicians that is both cognizant and capable of dealing with the data issues that arise from digitalization and its application to clinical process and outcome improvements.

In January 2014, our group hosted the Critical Data Marathon and Conference. In the Hackathon, physicians, nurses, and pharmacists were paired with data scientists and encouraged to investigate a variety of clinical questions that arise in the ICU. Over a 2-day period, over 150 attendees began to answer questions such as whether acetaminophen should be used to control fevers in critically ill patients and what the optimal mean arterial pressure is among septic patients. This event fostered relationships between clinicians and data scientists that will support ongoing research in the ICU setting. We currently plan for this conference to be a regular event and would encourage similar endeavors at other institutions.

Overall, the key contribution of the MIMIC database and the Critical Data Marathons is the promotion of ongoing, cross-disciplinary collaboration around learning. Clinicians, including nurses and pharmacists, are provided a platform to contribute to knowledge discovery that had been traditionally exclusive to academic researchers. Data scientists are thrilled by the opportunity to transform practice and improve health outcomes. Creating and fostering these partnerships across disciplines is non-trivial, given that their paradigms and practices are difficult to interlace into new and different contexts. However, the Critical Data Marathons simultaneously held at MIT, in London, and in Paris in September 2014 proved that this cultural shift is not only feasible but also replicable and scalable.

Next Steps/Discussion

We envision a learning system where knowledge generation is routine and fully integrated into the clinical workflow. The next step toward this goal is the introduction of formal courses into medical school and residency curricula. These courses will focus on skills needed to build, maintain, and analyze large data sets. The growing importance of Big Data in everyday clinical situations will be emphasized, and students will be given the opportunity to investigate clinical questions that have come up in the course of their clinical rotations.

In addition to the above curricular goals, medical schools and residency training programs need to develop new ways of incorporating data scientists into a multi-disciplinary approach to patient care. As Big Data becomes more accessible, individuals who can navigate and help analyze large data sets will become an increasingly important part of the care team. Physicians will need to know how to work with these professionals in ways that allow for meaningful conclusions to be drawn from large amounts of data in real time. Beyond partnerships formed in future Critical Data Marathons, we envision a program where data scientists from the MIMIC group will be able to join clinical teams for ICU rounds and participate in clinical decision making through the real-time analysis of Big Data.

The inclusion of data scientists as part of a multi-disciplinary team is one way to engender collaboration with the clinicians. This model has been successful with other healthcare professions, including pharmacy, physical therapy, and social work. Participating in rounds will provide data scientists an opportunity to work alongside clinicians and to receive immediate feedback to their input. Their addition to the team creates a substrate for potential innovation chain reactions that simply would not occur under other circumstances.

The time has come to leverage the data we generate during routine patient care to formulate a more

complete lexicon of evidence-based recommendations and support shared decision making with our patients. In this setting, the practice of every clinician will necessarily expand to participate in these issues. This must be done without creating enormous extra work for already overburdened clinicians. In contrast, the interactions of regular clinicians with a knowledge-generating system should be rewarding in both the intellectual and workflow senses. All clinicians will share the responsibility of creating a more complete knowledge base and transforming practice to improve care. The data are already being generated. Now is the time to train clinicians who can harness the true potential of this information to provide better care for our patients.

Acknowledgments

L.A.C. is funded by the National Institute of Health R01 grant R01 EB017205-01A1.

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Article

First (Expiration) Dates

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Synopsis: Certain provisions in the ACA are expiring soon, and those expirations will create room for further policy debate. We present three cornerstones of reform in this context that these debates will need to address in order to be viable: (1) prioritizing coverage, (2) evidence-based policy, and (3) public and private interdependence.

Introduction

Health care reform is not a discrete event that ended with the passage and implementation of the Affordable Care Act (ACA) in 2010. It is an ongoing process whose success depends upon the sustained involvement of policymakers, providers, patients, and other stakeholders. The provision on increasing Medicaid payments for primary care services encapsulates the decisions and challenges of continuous reform.

Beginning in 2013, the ACA used federal funds to temporarily raise Medicaid primary care payments to Medicare levels. These federally funded rate increases are due to expire at the end of 2014. On average, Medicaid fees were increased by 73%, although the magnitude varies by state (Zuckerman and Goin, 2012). Given the Medicaid expansion stipulated by the ACA and pre-ACA survey results showing only 70% of physicians would accept new patients with Medicaid compared to 96% who accepted new patients (Decker, 2012), increasing primary care provider participation in Medicaid has been viewed as an important step to ensuring the ACA's success in providing affordable health care. This is important despite counterarguments that Medicaid or uninsured patients receive equal attention at primary care appointments (Bruen et al., 2013). We dissect the intricacies of this argument in "Evidence-Based Policy" below. With PCP participation in mind, Senators Patty Murray (D-WA) and Sherrod Brown (D-OH) introduced a bill to extend the application of the Medicare payment rate floor until 2017. In response to the overall primary care physician shortage, OB/GYNs, nurse-midwives, NPs, and PAs will also be eligible for the payment increases. The bill has been referred to the Senate Committee on Finance; it is uncertain if it will pass in the Senate, and it is also unclear if it will pass in the Republican-controlled House.

The broader turmoil about the future of the ACA obscures some of these important—albeit less controversial—provisions and regulations of the landmark law. The ACA authorizes a variety of demonstration grants, changes to payment systems, and temporary programs that provide opportunities for continued reform without waging major political battles. Regulations are a key step in translating the ACA to changes in health care delivery. Built-in expirations and annual updates could mean these regulatory changes have far-reaching effects. We can maintain a path to improved health outcomes by further prioritizing programs that increase coverage, using data from rapid-cycle evaluations to drive our policy updates and resource allocation decisions, and continuing to balance public program investments and private sector innovations.

Prioritizing Coverage

Continued health care reform will inevitably involve further political conflict. Authorization and funding for existing programs that increase health insurance coverage should be prioritized. For example, the ACA approved CHIP funding only through September 2015. While there is substantial overlap between CHIP and the children who qualify for coverage through the ACA's health insurance exchanges, implementation of the exchanges has been significantly complicated. For example, individuals may purchase a health insurance exchange plan using federal subsidies if the cost of participating in their employer's insurance plans exceeds 9.5% of their income. However, this 9.5% affordability threshold only takes into account the premiums for the individual, not their dependents. This regulatory error has been termed the "family glitch," and until it and similar problems are resolved in the exchanges, CHIP

should continue to be funded, because without it, an estimated 1.9 million children would be without reliable coverage (Alker, 2014). Both funding CHIP and resolving regulatory issues in the exchanges require Congressional action; as long as there is a party split over the ACA, CHIP funding may be more politically feasible because it is not directly associated with the ACA.

The 2015 expiration of CHIP funding also presents an opportunity to streamline payment regulations and to think critically about the future of safety net coverage for children. Senator Jay Rockefeller's (D-WV) bill to fund CHIP through 2019 offers one vision: along with addressing the problem of premium stacking (wherein a family pays CHIP premiums in addition to exchange plan premiums), the bill expands eligibility and requires states to coordinate transitions between Medicaid, CHIP, and exchange plans. While lawmakers will debate funding and oversight, building on existing programs ensures that fewer Americans slip through without insurance. However, as we move forward with reform, passing what amounts to stop-gap measures should not take the place of negotiating the difficult legislative and regulatory hurdles necessary to streamline our health care payment system.

Evidence-Based Policy

Expanding safety net coverage in a cost-efficient way requires expanding access to primary care and preventative health services. However, it is not clear that increasing Medicaid primary care payments increases provider participation. Neither CMS nor State Medicaid offices have collected data on whether or not the payment increases are in fact attracting more primary care providers to Medicaid (Galewitz, 2014). While funding is important, access is the goal. Perhaps "Medicaid" carries an unshakeable stigma of unreliability for physicians or, in the context of expansion, seems like a federal overreach. A study from Washington State's 2011 survey of primary care professionals also highlighted administrative burden, patient complexity, and referral refusal as additional concerns (Long, 2013). Whatever the perception, policy informing continued changes cannot be drafted appropriately without hard data addressing some of the concerns beyond reimbursement.

Data-driven policy is also essential for reducing cost growth. Medicare Advantage payments are slated for a gradual reduction over 10 years, which the CBO estimates will save \$136 billion. Although Medicare Advantage has traditionally been viewed as an unsatisfactory policy (i.e., expensive and lacking in quality gains), a group at Harvard found that policy changes to Medicare Advantage from the mid-2000s have reduced adverse selection problems (Newhouse and McGuire, 2014). Prior to the 2003 Medicare

Modernization Act, enrollees were unable to switch out of restricted MA plan networks. This resulted in older, sicker, risk-averse enrollees staying in traditional Medicare—a hypothesis confirmed by a 15% mortality gap between traditional Medicare and MA (Medicare Payment Advisory Commission, 2010). In more recent briefings to Congress, MedPAC reports that CMS does not have sufficient access to claims data from MA plans in order to assess comparative mortality (Medicare Payment Advisory Commission, 2014). Given these findings and the large changes to Medicare reimbursement under the ACA—including the introduction of accountable care organizations (ACOs)—future evaluative work comparing Medicare Advantage, traditional Medicare, and ACOs will be essential as these programs come up for re-evaluation.

It is important to advocate for some caution alongside a push for data-driven policy. We should be aware data from newly implemented programs may not tell the entire story and that these data can be abused or misinterpreted to advance a given agenda. There is a necessary lag period as new programs start when appropriate assessment might not be feasible; providers, researchers, and policymakers must work together to balance the need for rapid evaluations and allowing enough time to gauge impact.

Public and Private Interdependence

Publicly funded programs (e.g., Medicare and Medicaid) and the private sector have complementary roles to play in creating and sustaining the ACA's payment and care delivery goals. Developing ACOs provides an example of how the public and private sectors can work in tandem. The goal of the federal ACO Shared Savings Program is to get providers to cooperate in assuming responsibility for the total cost and quality of a defined set of their Medicare fee-for-service patients. The Shared Savings Program has been key to getting less experienced provider groups involved in payment reform, and private insurer adoption of the model will be necessary to sustain the transition to value-based payment supported by the Shared Savings Program. While the majority of Shared Savings Program participants are only eligible for shared savings, early ACOs with private contracts appear to be more comfortable bearing downside risk for shared losses than public participants (Lewis et al., 2014).

This private sector buy-in is a boon to advocates for accountable care models. In addition to allowing provider groups to gain experience with managing risk, Shared Savings Program contracts are a relatively safe vehicle for testing private sector innovations such as Walgreen's ACOs embedding pharmacists in primary care teams to improve medication management. Interesting evolutions of the ACO model are appearing in private contracts, as well: Florida Blue and the

Moffitt Cancer Center have partnered to form a cancer-specific ACO. However, it is unclear whether this will lead to disproportionate market share and antitrust issues commensurate with the Partners expansions in Massachusetts (Farragher, 2014). A recent review of ACOs argues for size limits and incentive structures beyond what current groups practice. It suggests that ACOs cannot be more efficient than current payment models if they do not follow these prescriptions (Frandsen and Rebitzer, 2014). These reform mechanisms therefore must be monitored closely to prevent unintended consequences such as the creation and exploitation of loopholes around competition laws.

Conclusions

Reform is not stagnant. It relies on changes in public attitude, personal choices, and unifying legislation. “Health outcomes,” however, is necessarily longitudinal, so no claims about the current law’s impact can be validated yet outside the framework of coverage and access (Blumenthal and Collins, 2014). To maximally improve our health care system over time, the practices we advocate for here—universal access, evidence-based policy, and public-private partnerships—should be routinely incorporated in both academic and political processes.

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Article

Post-ACA Healthcare Financing Reform: Vermont Leads the Way

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Synopsis: The U.S. Third Party Payment system of healthcare financing is inefficient when compared to those of other developed economies. The Affordable Care Act, while further institutionalizing many elements of this system, also provides a mechanism for state experiments in systemic payment and care delivery reform, with Vermont leading the way.

A Changing U.S. Insurance Landscape

In March of 2014, the White House completed a major media and public relations campaign encouraging Americans to sign up for health insurance coverage in the first of the Patient Protection and Affordable Care Act's (ACA's) consumer enrollment periods. From the administration's perspective, the effort—though technologically troubled—was a numerical success, with a recent study showing that more than 10 million Americans likely received coverage, either through state or federal exchanges or Medicaid (Sommers et al., 2014).

While questions remain, particularly around the issue of patient access in light of the “narrow networks” sometimes offered as a part of exchange plans, the law unequivocally achieved a number of laudable improvements in both the issuance of and access to health insurance. Principal among these improvements were guaranteed issue for those with pre-existing medical conditions, the elimination of insurance rescission, and increased access to Medicaid for the working poor. Also promoted as a mechanism for lowering health care costs, the ACA was implemented during a sustained period of unusually low health care cost growth (Dranove et al., 2014). This timing, combined with the difficulty of disaggregating factors that affect national healthcare spending, will make cost savings claims difficult to prove.

The ultimate test, of course, of a law titled, in part, the Affordable Care Act, is whether or not medical care (rather than insurance, which is an intermediate measure) is truly affordable for the consumer. The ACA, calcifying structural administrative inefficiencies in the United States' health care financing system, is not a beacon of hope in this regard. Vermont, however, has chosen to take advantage of a provision of the law that allows states to enact new health care financing systems. As the first state to invest substantial resources in creating a novel financing system, Vermont serves as a public test case for broader health care financing reform.

Burdens of Administrative Costs in Healthcare

Those in the U.S. not covered by a government program like Medicare or the Veteran's Administration are health care consumers in a Third Party Payer system, a financing arrangement characterized by a long, complex sequence of financial and administrative transactions between patients, insurers, and health care providers. As the U.S. Institute of Medicine has reported, one of the major failures of our Third Party Payer system—a system in which both health care dollars and paperwork change hands substantially more than in other developed economies—is the cost of billing and insurance administration (Smith et al., 2013). A widely cited 2003 study in the *New England Journal of Medicine* showed that in 1999 health administration costs totaled in \$1,059 per capita in the United States, a threefold multiple of the \$307 spent per capita in Canada (Woolhandler et al., 2003).

In today's terms, that means that the United States spends an unnecessary \$350 billion or more per year due to our byzantine payment scheme. To place this number into perspective, at nearly 10% of our national health care spending, \$350 billion represents an amount capable of effecting dramatic change in our health care system's affordability, accessibility, and cost; it could pay, annually, for each Emergency Department visit that does not end in a hospital admission, or every visit to a doctor's office (Agency for Healthcare Research and Quality, 2011). And this number will likely rise in coming years, as all plans offered through federal and state exchanges are participants in the inherently administratively inefficient Third Party Payer system.

International Financing and Payment Systems

The United States has a singular but not totally unique health care financing and administrative system (Götze

and Schmid, 2012). While other developed nations, such as Germany and Japan, use Third Party Payment, they also invariably employ two powerful tools of administrative simplification absent from the U.S. system: central price controls or negotiations and a high degree of plan uniformity. The ACA's four plan tiers point in the right direction vis-a-vis plan design, yet it is important to note that even the most optimistic numbers of those covered through the ACA represent approximately 5% of Americans, meaning that the vast majority of insured persons are subject to little plan design standardization beyond those imposed by Essential Health Benefits provision of the law. Individuals covered by Medicare or Medicaid—approximately 30% of Americans—also have plans with a high degree of administrative uniformity (DeNavas-Walt et al., 2013). This proportion stands in stark contrast to other countries with third party payment. In Germany, for example, the ratio is nearly reversed; nearly 90% of citizens are covered under a single statutory plan design (Deloitte Center for Health Solutions, 2010).

Consumers ultimately bear the administrative costs of healthcare, which vary both internationally and domestically depending on their underlying financing scheme. Health system administrative costs in Canada, for example (under a National Health Insurance program), are one third those in the United States (Woolhandler et al., 2003). Domestically, total costs of administering Medicare (a single-payer-like program) have grown substantially slower than those of private insurance (Centers for Medicare and Medicaid Services, 2013). And health care providers incur additional costs of time and money in the third party payment system; doctors in the United States spend nearly four times the money interacting with payers when compared to their counterparts in Canada (Morra et al., 2011). And while substantial debate continues about the proper interpretation of these costs in both models, a fact beyond dispute is that the United States spends much more to generate poorer health outcomes (Davis et al., 2010), and there is substantial evidence to implicate our unique financing system in this failure.

Vermont's Innovation

Given that our payment system incentivizes utilization, costs more, and does not generate better population health, what options present themselves for changing a deeply rooted financing paradigm? A 2012 Department of Health and Human Services regulation providing individual states the ability to petition for "Waivers for State Innovation" may provide the substrate for a natural experiment. In practical terms, these waivers require that any financing scheme enacted by a state must establish that its reform plan would provide coverage that is (1) at least as comprehensive as that mandated by the ACA, (2) is at least as affordable as ACA coverage, (3) covers at least as many residents as

the ACA would have covered, and (4) does not increase the federal deficit (The Federal Register 76, no. 49, 2011).

This provision of the law allowing states to create new financing and care delivery systems is to be applauded, and one state is forging ahead with fundamental healthcare payment reform: Vermont. A team led by Harvard economist William Hsiao—a key policy contributor to Taiwan's 1995 transformation to a single-payer system—projected the state to save approximately 25% annually in its total healthcare spending (a total savings of \$4.6 billion in the first 5 years), with a substantial concomitant statewide macroeconomic stimulus. Hsiao's projected savings would come principally from lower administrative expenses, with 40% of total savings generated by "payment reform and integration of delivery system" (Hsiao et al., 2011).

Though projected savings are substantial, Vermont faces challenges in financing the transition. The state's total healthcare bill is projected at \$5.9 billion, of which \$1.6 billion is necessary as new, incremental revenue (Wakely Consulting Group, 2013). This represents a substantial sum when compared to the state's total 2013 revenues of \$5.4 billion (Vermont Comprehensive Annual Financial Report For the fiscal year ending June 30, 2013). Practically, this means that must find both the means and political will to increase tax revenues by nearly 30% before 2017.

Hsiao's Taiwan experience is also not perfectly analogous; Vermont, as a small state in a union characterized by high interstate mobility, stands in geographic contrast to Taiwan, an island nation state. This means that Vermont will likely see some amount of cross-border medical traffic—those patients bringing with them traditional health insurance coverage—lessening potential administrative savings. Substantial interstate mobility also exposes Vermont to some degree to adverse selection risk; individuals or families with low income but high expected medical costs could conceivably pay less under Vermont's payroll-financed system than under the ACA's premium-based scheme. Both of these risks are diminished, though not eliminated, however, with the combination of guaranteed issue and Medicaid expansion as core provisions of the ACA. Finally, Vermont has not yet found the political will to enact substantial medical tort reform, a feature crucial to the new system's success, according to Hsiao et al. (2011).

Canada: A Lesson Adjacent

Taiwan's victories in both coverage and cost (Lu and Hsiao, 2003), though, are reason to remain hopeful for the eventual successes of Vermont's single-payer healthcare, should it come to pass. And if it does, the prospects for Vermont's experiment gaining national traction may have historical parallels in the evolution of

Canada's health care financing and administration. The Canadian Medicare system (equal in name only to the U.S. Medicare system)—often mistakenly thought of as national from its inception—also began with a single-state vanguard. State-managed healthcare in Canada began in Saskatchewan with the passage of 1916 legislation providing for state-salaried doctors. The system was further solidified with enactment of a 1947 Saskatchewan hospitalization program covering all residents. And from these provincial beginnings, nearly 20 years would pass before Canada had the beginnings of the national Medicare system seen today, codified in the Medical Care Act of 1966 (Marchildon and O'Fee, 2007).

Doctors in Vermont, as a key constituency of health financing reform (and necessary as a practical matter of care delivery), must be convinced that a single-payer system is not a harbinger of reduced professional autonomy or professional financial decline. Fortunately, though, in Canada, concerns of government control over health care decisions and declining reimbursement have both proven poorly founded. Canadian health records remain privileged information between physician and patient. Financially, national health care has, if anything, raised the relative wages of doctors; in the 5 years preceding the introduction of the national health care system, physicians' incomes averaged 33% greater than the average for other professionals. In the 5 years following the introduction of Medicare, their incomes increased to 47% above those of other professionals (Comanor, 1980).

Both policymakers and doctors in Vermont would do well to take note of the Canadian experience; the Canadian path to robust health care financing transformation was not only iterative but hard won. British Columbia attempted to create its own Health Insurance Act in the 1930s, but the effort was short lived. Doctors rallied their political will en masse and ensured its demise. Doctors in Canada have also demonstrated beyond the ballot, with major strikes preceding the expansion of state involvement in healthcare at each step, with smaller, local strikes occurring on a reasonably frequent basis (Stevenson et al., 1988). These setbacks have ultimately forged a system, however, in which doctors—often wary of payer consolidation accompanying financing reform and its attendant reimbursement leverage—have retained their proverbial “seat at the table” in annual fee-schedule negotiations.

The Path Ahead

While powerful forces (structural economic inertia not the least of these) have contributed to the widespread sense of inevitability surrounding the United States' health care financing system, many of the greatest ideas to come from this country have been refutations of

established practices or norms. We are, of course, a nation borne of the refutation of an idea. There is hope that Vermont may provide one more tally in that long list, and that further experiments, whether they be in single payer or other new models of health care financing simplification, follow. So while it is too soon to tell if Vermont's transformation will prove successful—or even take place—the greatest success of the Vermont initiative lies in its very experimentation: one state's attempt to enact profound change in health care financing and delivery by using the capacity for systemic change contained within the ACA, a law that in general codified “health financing as usual.”

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Article

Bridging Access

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Synopsis: While the effect of the Affordable Care Act has yet to be fully measured, early results indicate legislation will not be felt on the ground, as certain populations still lack healthcare. In Miami-Dade and Dallas-Ft. Worth, for example, significant geographic and cultural barriers exist which prevent populations from accessing healthcare. This article examines the possible use of mobile clinics to offer temporary relief to these populations until more permanent measures may be constructed, such as Federally Qualified Health Centers.

Sometimes we need more than just a bridge.

When people mention the City of Palo Alto, they rarely speak about healthcare. Instead, you'll usually find a 20-something talking about his or her start-up or new endeavor with Facebook or Google. Yet less than 3 mi away, across the University Avenue bridge, exists a shocking juxtaposition. On the east side sits East Palo Alto, a town that struggles with crime, poverty, and the uninsured, while the west contains one of America's most luxurious accommodations: the Four Seasons Hotel.

While nearly 40,000 cars cross the bridge every day, healthcare rarely traverses the gap.

Take Mr. Sanchez*, a patient at Arbor Free Clinic in East Palo Alto with pain in his mouth.

This 58-year-old male sought treatment for the pain in his upper right molars that started three weeks ago. What he did not voluntarily present was his backstory.

Upon physical examination, he was flushed, fatigued, and contained a dental abscess surrounding his upper right molars. Twenty-two of his thirty-two teeth were missing, and he had signs of recurrent infections in his gums. It quickly became apparent that the pain in his teeth was an acute sign of a much larger, chronic problem.

Have you seen a dentist Mr. Sanchez?

No.

How about a physician?

Yes.

When?

Six years ago. Mexico.

My heart sunk a little.

How about a physician here?

No.

You said the pain started three weeks ago?

Yes. *Very bad.*

May I ask why you have not seen a physician sooner?

No time. I need to watch my kids, see my parents.

Is there someone else who can help with your parents and children?

No.

Upon eliciting a further social history, I found that Mr. Sanchez was a Spanish-speaking 58-year-old single parent working two construction jobs to support his three children and parents, both of whom were diagnosed with terminal cancer.

We gave him acetaminophen and a prescription for penicillin for the dental abscess. He refused to take a referral for a primary care physician or for a dentist. He did not have the time. In fact, he needed to go back to work later that afternoon, having traveled to Arbor Free Clinic by riding with two friends, and coming from nearly 30 mi away. Without further treatment, he would likely lose his right molars too.

Unfortunately Mr. Sanchez's case is not an isolated occurrence. Those who are underinsured or uninsured are often overworked, overstressed, and overdue for healthcare—and the problem seems to be getting worse.

Five of the nine counties in the bay area have more than 10% of their population uninsured: San Mateo (14.7%), Contra Costa (11.4%), Sonoma (11.2%), Alameda (10.3%), and Santa Clara (10.2%) (Figure 1). The town of East Palo Alto, where Arbor Free Clinic is based, has an uninsured rate of 25.9%, or over one in four individuals—the highest among any municipality in the bay area. In addition, the problem has been consistently increasing across the entire nine county bay area, with the number of uninsured increasing from 9.4% (577,000) to 10.9% (668,000) between 2007 and 2012 (CHIS, 2012).

Perhaps even more alarming is that the San Francisco bay area fares better than most of the United States. In fact, the city of San Francisco, thanks to its Healthy SF program, has an uninsured rate of less than 5%. This is in sharp contrast to other major US metropolises that have much higher uninsured rates: Miami-Dade (34%), Dallas-Fort Worth (31%), Los Angeles (25%), Houston (20%), New York (15.7%), and Chicago (11%) (Figure 2) (DeNavas-Walt et al., 2012). Only Boston has a lower uninsured rate, at less than 4%, due in part to the health care reform initiative of 2006 enacted by the state of Massachusetts.

While the effects of the Affordable Care Act (ACA) have yet to be seen, it is doubtful that federal legislation will be felt on the ground, as a recent study estimates that a large portion of the uninsured in the Bay Area (563,000/668,000; 84%) are undocumented immigrants who do not qualify for the state's healthcare insurance, MediCal (CHIS, 2012). And while more community clinics are being built, the bay area has only approximately 15 truly free clinics—of which most have limited hours and services.

Additionally, many of the free clinics are limited in whom they can help due to geographic location or transportation barriers. A study conducted by the Washington State Department of Health found that individuals are willing to travel 8.6 mi to find routine care, on average. This, however, includes individuals who own cars and have the ability to travel in vehicles (Yen, 2013). If we examine individuals who must walk, a study conducted by the Minnesota Department of Health found that people are only willing to walk 1.5 mi (Iacono et al., 2008). This leaves extensive gaps in coverage not only across the San Francisco Bay Area but also across the entire country that free clinics simply cannot fill alone.

So what then can be done to help the uninsured who do not qualify or are ineligible for medical insurance under the ACA? An obvious answer would be to increase the number of free clinics. This, however, is an arduous process, requiring months if not years of resource gathering and labor. In addition, getting governmental approval through Clinical Laboratory Improvement

Amendment waivers and county as well as state permits is an uphill battle, to say the least.

Mobile clinics may offer a solution to the dilemma. According to the Mobile Health Map, an estimated 2,000 mobile clinics receive approximately 6.5 million patient visits each year. These custom vehicles are spread throughout the United States and provide a wide range of services, including primary, secondary, and specialty care. One recent study conducted in Massachusetts on the Boston "Family Van" found that blood pressure was significantly reduced (systolic/diastolic differential: 10.7/6.2 mmHg) in those individuals who visited a free mobile health van between 2010 and 2012 (5,900 unique patients; 10,509 visits). In addition, according to patient surveys, a large number of emergency department visits were also avoided. The same study estimated the annual cost savings from this mobile clinic to be over \$3.1 million through a reduction in emergency department visits and prevention of acute illnesses (Song et al., 2013).

Indeed, further studies within the United States must be done to confidently say that such an approach would help improve healthcare access and the situation of the uninsured. Although many major metropolises have large pockets of residents that lack health care access, each situation may be surprisingly unique. Miami-Dade and Houston, for example, with uninsured rates of 34% and 20%, respectively, may suffer from cultural and lingual barriers, as a large portion of the uninsured (37%) are Spanish-speaking Hispanics (Gee, 2014). In addition, many individuals simply do not wish to enroll or are ineligible for state Medicaid. A mobile clinic that provides free healthcare to these individuals can serve a combined role of enrolling individuals in free or sliding fee clinics, determining eligibility under the ACA, and providing much needed healthcare.

Other metro areas have fewer cultural and language obstacles but more geographic barriers to accessing healthcare. The South Central neighborhood of Los Angeles, for example, has an uninsured rate of 52%, one of the highest in the nation (CHIS, 2012; Steinhauer and Morris, 2007). Unfortunately this 50.1 mi² region within Los Angeles also has a dearth of hospitals, with MLK Jr.-Harbor hospital closing in 2008 and the next hospital not scheduled to open until late 2015. A free mobile clinic could serve to improve geographic healthcare access to urbanized pockets such as South Central Los Angeles while also educating individuals about the benefits of Medicaid and the ACA (Steinhauer, 2008).

The Dallas Ft. Worth and Houston metropolitan areas, on the other hand, showcase what happens when states refuse to expand Medicaid coverage. After Texas decided against expanding its Medicaid coverage, many of the city's residents fell into what is being called "the new

doughnut hole,” (Berard, 2014). Under Texas Medicaid, for a family of four to be covered, the household cannot make more than \$298 per month, or approximately \$9.60 per day. The ACA envisioned expanding state Medicaid eligibility up to an annual household income of 133% of the federal poverty level (FPL), which is \$11,170 for an individual or \$23,550 for a family of four. The ACA also provides stipend assistance to those who fall between 400% (\$88,020 for a family of four) and 133% (\$29,326.50) of the FPL. With state refusal to expand Medicaid coverage, many individuals make too little to qualify for stipend assistance but too much for state Medicaid. In the case of Houston and Dallas-Fort Worth, that means any family of four that makes more than \$3,756 and less than \$29,326.50 automatically does not qualify for any federal or state insurance and lacks healthcare access (Heberlain et al., 2013). In the Dallas-Fort Worth and Houston metros, an estimated 1 million individuals now fall into this category (Berard, 2014). Again, a coordinated set of free mobile clinics with a strong referrals system could help relieve the situation as well as educate local populations about free and sliding fee clinics that offer more extensive services. Such is being done at the Cardinal Free Clinics (CFCs) affiliated with Stanford University School of Medicine in the San Francisco Bay Area. The CFCs mobile health team (formally known as the CFC Screen Team) works in the community regularly with shelters, community centers, and food banks to offer healthcare and provide referrals for patients to surrounding clinics in an attempt to increase healthcare access. Since the initiative started last August, over 2,000 individuals have been visited by the mobile health team, and the number of patients at two stationary CFCs in East Palo Alto and San Jose has nearly doubled on a weekly basis.

While these results are encouraging, it should be noted that mobile free clinics are only a temporary relief for areas that lack healthcare access due to geographic, cultural, or insurance barriers. A more permanent solution would be to establish a freestanding federally qualified health center (FQHC). FQHCs receive expense reimbursement from the Bureau of Primary Health Care and the Centers for Medicare and Medicaid services under the Public Health Service Act for admitting uninsured and low-income individuals. FQHCs have been a large success in medically underserved areas, both in rural and urban settings.

Unfortunately due to limited government funding, the United States only has a little over 1,200 FQHCs currently, and many more are needed to fill in healthcare gaps. Furthermore, the obstacles to becoming a FQHC are immense. First, clinics and health centers must acquire a sufficient number of physicians and healthcare workers to operate. Second, they must have an established history of serving an underserved community or demographic, a feat that is neither

profitable nor sustainable without external assistance. Third, they must receive a section 330 grant from the Federal Government. There are large costs associated with starting a FQHC before an organization even becomes eligible for federal funding from a section 330 grant. In fact, on average, it takes between 5 and 7 years for a clinic to transition to FQHC status, if successful (HHS, 2011).

While this may seem like a taunting task, the ACA has recently helped make it easier for clinics to transition to FQHCs by increasing the amount of available funding for FQHCs by \$11 billion. While free mobile health clinics are by no means the end all solution, they can offer temporary relief to neighborhoods in the time it does take to establish a FQHC, as they typically only take 3 to 6 months to become fully operational (Hill et al., 2014). Therefore, free mobile health clinics offer a viable solution to help address issues of healthcare access and uninsured within both urban and rural areas while more permanent measures are enacted, such as FQHCs. Such temporary measures are vital for neighborhoods such as South-Central Los Angeles and Miami-Dade county, where more than one in four individuals who lack insurance coverage also lack proper healthcare access (DeNavas-Walt et al., 2012).

*Mr. Sanchez is a fictitious name provided by the author in accordance with the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

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Opinion

Lethal Injection and Medical Ethics: Physicians in the Execution Chamber

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The opinions expressed in this piece are solely those of the author. We welcome counterpoint submissions to be published in future issues.

Synopsis: The advent of several recently botched executions has sparked debate over the practice of lethal injection in America. One interesting facet of this debate relates to the ethics of physician involvement in the practice. Here, a rule utilitarian argument against physician involvement based on patient consent is presented.

Introduction

In all 38 U.S states where capital punishment is legal, the preferred method is lethal injection. In total, 17 states require physician involvement, and 18 permit it (Black and Sade, 2007). For years, scholars have contested the physician's role in this practice, but disagreement persists about the ethical reasoning involved. Several "botched" executions in states undertaking drug protocol changes have garnered substantial media attention (Porter, 2014; Pearce and Susman, 2014; Connor, 2014; Allen, 2014). Reports have detailed the unintentional but gruesome outcomes inmates can suffer at the hands of prison staff and medical professionals (Allen, 2014). Ongoing questions surrounding drug efficacy have fueled public debate and have led to high-profile legal cases (Associated Press, 2014; Denno, 2014; *Base v. Rees*, 2008). In this commentary, I will argue physician involvement in lethal injection procedures is unethical, even if legally permissible, as it encroaches on the patient's right to informed and un-coerced consent. Physicians have an obligation to defend patient rights and abandon practices that infringe upon them.

Consent

A well-established tenet of both US law and medico-ethical standards is the patient's right to give informed consent prior to a medical procedure (Fisher, 2013). Although inmates do lose certain rights upon conviction (mobility rights, civil freedoms, etc.), they still hold fundamental human rights including those related to informed consent. Consider the United Nations Office on Drugs and Crime and their statement on the issue of HIV testing in prisons: "...prisoners may be treated as if they were HIV-positive and lose privileges unless they submit to HIV testing. Such mandatory or compulsory forms of HIV testing violate ethical principles and the

basic rights of consent, privacy and bodily integrity" (UNODC/UNAIDS/WHO, 2009).

When it comes to the lethal injection question, some have suggested that a physician could "easily condition his or her participation on the prisoner's consent to his participation" (Nelson and Ashby, 2011). This reasoning does not reflect the elements of forcefulness and coercion at play in death penalty cases, which make any meaningful consensual practice impossible. In the case of lethal injection, the prisoner is forced into the procedure, and so considerations based on the legitimacy of the aforementioned "consent" are nonsensical, given that no decision-making or consent powers exist in the first place (Boehnlein, 2013). Consider Beauchamp and Childress (2001) and their seminal work on coercion and autonomy:

"Coercion occurs if and only if one person intentionally uses a credible and severe threat of harm or force to control another. ...A physician in a prison who tells an inmate he must submit to sedation may need an accompanying prison guard for the threat to be credible and for coercion to occur. [...] Coercion occurs only if a credible and intended threat displaces a person's self-directedness. Coercion voids an act of autonomy; that is, coercion renders even intentional and well-informed behavior nonautonomous."

Physicians who involve themselves in practices such as lethal injection are infringing on the prisoner's rights of consent and bodily integrity as well as on the ethical principle of non-maleficence ("do no harm"). Even if we accepted the notion that physicians could condition their participation on the prisoner's consent to his or her participation, such consent would be void due to coercion. It is not the imminent death of the patient, in and of itself, that makes the situation coercive. For

example, terminally ill patients face imminent death, yet active euthanasia practices can be completed with informed consent. Here, the coercion lies in the fact that the only viable alternative to the physician's intervention includes the threat of a painful and potentially gruesome death at the hands of less-qualified prison staff. Either way, a physician who intervenes in these practices is one who infringes upon the medically relevant rights of the prisoner.

Legality and Morality

Proponents of physician intervention appear to be under the illusion that the debate over the moral and ethical legitimacy of capital punishment is not settled. They argue that since capital punishment is legal in certain states, physician intervention is ethical by default. However, the legal permissibility of an action does not in and of itself give a definitive answer as to whether or not a physician's involvement in that action is ethical.

Consider a hypothetical state where a form of torture such as water-boarding is legal. In this scenario, a case favoring physician involvement in torture could be made analogous to the case for physician involvement in lethal injections. For instance, a physician could monitor vital signs or administer drugs as needed, ensuring the prisoner does not die in the middle of an intelligence recovery operation (Miles, 2006). But is there a line to be drawn? Should laws not condemn physicians who refuse to uphold ethical standards instead of encouraging them? It is likely that many proponents of physician involvement in lethal injection would not endorse involvement in torture with such ease. It is the forfeiture of consent that makes the example of torture seem especially egregious but equally makes physician participation in capital punishment unethical.

Rule Utilitarianism

One of the most compelling arguments in favor of physician intervention asserts that regardless of whether capital punishment is fundamentally unjust, physician involvement is nevertheless ethically permissible when the goal is to optimize comfort and minimize suffering for death row inmates facing execution. Given their medical expertise and extensive training, no other professionals within our society could carry out, oversee, and ensure the comfort of the prisoner as efficiently.

This line of reasoning relies on the philosophical doctrine of utilitarianism; often termed the "greatest good for the greatest number" (Bentham, 1907). Arguing in favor of intervention with respect to such cases seems to make sense from an act utilitarian point of view. A prisoner has been sentenced to death, and a physician can minimize the pain associated with the procedure. But problems arise when this philosophy is used to

defend intervention in any case of lethal injection, as it assumes physicians are powerless in the face of established but unjust or unethical laws. Further, this position assumes defending medical ethical norms related to patient consent in the long term is unimportant or at least less important than mitigating pain in the short term. However, in democratic societies, public opinions (including those espoused by health care professionals) change laws. In addition, it has been asserted that defending ethical principles within the medical profession is crucial to ensure sustained levels of public trust in the profession (Black and Sade, 2007). Considering these arguments, it seems that physicians may have an obligation to follow a rule against participation when it comes to lethal injection, in order to ensure the "greatest good for the greatest number."

Conclusion

Utility calculations in a single case with a single prisoner, admittedly, seem easy. But when we realize that the act of intervening in this one case may play a part in prolonging the acceptability of a practice that tears at the fabric of standard medical norms by disregarding the importance of patient consent, the utility calculation changes. The result is a crude but easy decision for physicians weighing the pros and cons of intervention. If one admits that medical professionals, as a rule, should not use their expertise on truly non-consenting individuals, it seems one must admit that physicians have an obligation to act as a silent protester in a democratic state. They can do this by avoiding participation in lethal injection practices. Just as Americans have traditionally said, "We do not negotiate with terrorists," physicians should declare, "We do not perform interventions on truly non-consenting individuals."

Acknowledgments

The author would like to thank Dr. Robert MacDougall for his suggestions and comments on earlier drafts of the manuscript as well as Dr. Ken Oakes for his editing of the manuscript. The author would also like to thank the editorial team at the Harvard Medical Student Review and the reviewers for their time and effort in improving the quality of the manuscript.

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Opinion

Too Much Sympathy for the Devil

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The opinions expressed in this piece are solely those of the author. We welcome counterpoint submissions to be published in future issues.

Synopsis: Complementary and alternative medicines permeate health care today, yet undergraduate medical education fails to appropriately inform students of such therapies. Critical evaluation of CAM is necessary to produce well-informed physicians who are capable of providing evidence-based care.

During orientation week of first year medical school, the class visited small communities to experience how rural medicine was practiced. Here, we toured through the services these community health centers offered: physiotherapy among them. The first physiotherapist demonstrated how he treats patients with ankle injuries by mobilizing the affected joints. The second physiotherapist explained how he uses acupuncture to treat his patients' pain by unblocking the flow of *qi* through their meridians. The third proudly displayed her magnet therapy machine, which she claims can cure anything from chronic arthritis to cancer. I knew immediately that one of these things was not like the others; one of these things didn't belong.

Since I had completed my undergraduate degree in Life Sciences, I had developed a rather acute sense for questionable claims: those that don't seem consistent with a scientifically informed view of the world. Nevertheless, I did my due diligence and looked into the evidence for these therapies. Joint mobilization is a legitimate treatment for ankle injury, decreasing time to return to pain-free movement, increasing function, and increasing range of motion (Green et al., 2001; van der Wees et al., 2006). Acupuncture, on the other hand, has failed to demonstrate efficacy in high-quality clinical trials using appropriate controls (i.e., sham acupuncture) for its major uses: low back pain, knee osteoarthritis, and migraine headaches (Ahn, 2013). Magnet therapy was more difficult to evaluate, due to the ambiguity of the claim and the general lack of evidence, but numerous studies found showed no benefit in the use of magnet therapy for patients with chronic low back pain, wrist pain (carpal tunnel), osteoarthritis, and motion sickness (Panush, 2013; Priesol, 2014; Kothari, 2013).

One of these things was not like the others; only one of these things was supported by evidence. I only knew this for certain because I went to the literature, but how many of my colleagues were less skeptical than I? How

many future physicians trusted that their medical program would present to them only evidence-based therapies? How many are unable to identify a complementary or alternative medicine and distinguish it from an evidence-based medicine?

Later on in the year, I found myself at odds with some of my colleagues when the topic of complementary and alternative medicine (CAM) was raised. Having done extensive reviews of the existing literature around many CAM therapies, I knew that supporting evidence was scarce—to me this point was paramount; I took issue with the fact that most CAM therapies remain unproven and in some cases disproven. My colleagues, however, were more concerned with the effect that failing to support CAM would have on a physician's relationship with their patient. They feared that if they were to criticize CAM in front of their patients who use it, the patients would feel alienated or distrustful toward the physician. My colleagues were so concerned with this that they seemed not to care whether or not the therapies they endorsed actually work. I believe that this reflects the structure of our undergraduate medical education (UME).

In medical school, we are taught that one of the most important skills to acquire is the ability to cultivate a trusting, honest, and non-judgmental relationship with your patient. This is undoubtedly an important characteristic, but it has been emphasized to the point that my colleagues were unable to approach the subject except in the context of the doctor-patient relationship; evidence, efficacy, and even safety had been put on the backburner. The result of this is the stagnation of academic discourse on the subject of CAM; it has become a topic people fear to criticize.

The purpose of medical school is not to produce physicians who forge strong relationships with their patients; the goal (according to the Royal College of Physicians and Surgeons of Canada) is to become a

multi-faceted professional according to the CANMeds competencies, one of which is the role of health advocate (The Royal College of Physicians and Surgeons of Canada, 2005). To me, being a health advocate means not only favoring policies and practices that benefit health but also advocating against policies and practices that could have a detrimental effect. The American Medical Association Code of Ethics states, "It is unethical to engage in or to aid and abet in treatment which has no scientific basis and is dangerous, is calculated to deceive the patient by giving false hope, or which may cause the patient to delay in seeking proper care" (American Medical Association, 1996). I have not been able to find an analogous provision from the Canadian Medical Association. The closest recommendation in the CMA Code of Ethics is item 23: "Recommend only those diagnostic and therapeutic services that you consider to be beneficial to your patients or to others..." However, this is a provision based on the opinion of the physician, rather than the evidence (Canadian Medical Association, 2004).

Ultimately, I believe that this imbalance in the attitudes of medical students can be remedied by directly addressing CAM in UME. Several surveys have investigated medical students' views on CAM, and all report that students have insufficient or no knowledge and understanding of the principles, efficacy, and safety of various CAM therapies (Chez et al., 2001; Hopper and Cohen, 1998). This is a problem since 70%-75% of Canadians report using CAM at least once, and 40% of Americans report using it in the past 12 months, and future physicians will need to make health care decisions involving CAM and have little or no formal instruction on it (Esmail, 2007; Barnes et al., 2008). Even physicians in current practice feel unprepared regarding CAM; according to a 2004 survey of California physicians, 61% do not feel sufficiently knowledgeable about CAM safety or efficacy, and 81% would like to receive more education on CAM (Milden and Stokols, 2004).

Physicians should be required to know, at least, basic information on the more popular CAM therapies (e.g., chiropractic, homeopathy, naturopathy, acupuncture, etc.), including the following: (1) the core beliefs and principles of the therapy; (2) a strict definition of the therapy¹; (3) the evidence surrounding its efficacy; (4) the evidence surrounding its safety, including special populations who may be at increased risk compared to the general population (e.g., patients on warfarin can have life threatening interactions with Ginseng, a naturopathic remedy marketed as *COLD-FX* (Vázquez and L. Agüera-Ortiz, 2002); and (5) who typically uses it and for what purpose. A well-planned course during medical school could easily make a generation of physicians more aware and informed about exactly what other medical advice their patients might be receiving.

Medical students need to be more adequately prepared to critically evaluate therapies and draw conclusions accordingly. I consider evidence to be the pillar upon which conventional medicine is built, and the only thing that raises it to a higher standard of quality and reliability than every other healing practice that has arisen throughout human history. I believe that with the appropriate emphasis on evidence built into their education, future generations of physicians can be more shrewd and critical, not just of CAM, but of all therapies and questionable practices. This next generation can be true physician advocates that oppose unscientific medical practices on a policy level and enable patients to make informed decisions regarding treatment, whether in favor of the evidence or not. If the priority is placed, however, on maintenance of the doctor-patient relationship, at the cost of ignoring the evidence, we no longer have the right to call what we do evidence-based medicine.

¹Strict definitions are important because CAM is so easily misrepresented. Acupuncture, for example, specifically refers to targeting meridians with needles to alter the flow of Qi; however, many use the term to refer to any type of needling (not on meridians), which is what well controlled studies call "sham acupuncture."

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