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The incredible rock layers of Zion are part of a system eroding the sedimented and lithified Navajo Sandstone. The remarkable rock of Ages was formed by millennia of cascading water cutting through and to the Grand Canyon. The rock layers are 2,000 feet thick in Zion National Park in Utah. This photograph was taken of Zion in 1967.

The authors randomly assigned patients with Stage 4 or chronic kidney disease who had not yet begun renal dialysis to 2 of the groups. The last group received an additional nephrology consultation with an interdisciplinary team and reported help in forming a treatment plan. All were satisfied, and had the opportunity to thoroughly discuss questions. They had a decrease in beginning dialysis, clinic visits, hospital admissions, days hospitalized, and emergency room visits.

34. Nasal Methylcellulose-Resistant Staphylococcus aureus Polymerase Chain Reaction: A Potential Useful in Guiding Antibiotic Therapy for Perinatal Neonates. Jennifer A. Johnson, MD; Michael E. Pilz, MD; Craig Nelson, PhD, CLS; Julie Ann Sortais, LCSW; Pushkar Chand, MD; Joseph E. Sherger, MD, MPH; David L. Shenson, MD

This is a retrospective study of adult patients admitted to a large urban hospital who had a nasal methicillin-resistant Staphylococcus aureus (MRSA) polymerase chain reaction (PCR) test and a lower respiratory tract culture within 48 hours of admission that the culture yielded Staphylococcus aureus. Results showed high sensitivity (93.3%) and negative predictive value (92.6%) of nasal PCR for MRSA in the lower respiratory tract. A nasal MIP PCR test could guide the discontinuation of MRSA-directed empiric antibiotic therapy in patients who are unlikely to be infected with this organism.

SOUL OF THE HEALER


Music and Medicine: A New Horizon. Nicholas Merrill

The Permanente Journal is happy to announce the availability of Continuing Medical Education credits for completing manuscript reviews for The Permanente Journal. Physicians are now eligible to receive up to 15 AMA PRA Category 1 Credits per year (3 AMA PRA Category 1 Credits per manuscript). With this change, we have launched our new For Reviewers home page on our Web site: www.thepermanentejournal.org/reviewers.html.

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94 No Laughing Matter.
David E Clarke, MD, FCCP

A cough, then breathlessness; laughter then breathlessness. Is the cause the tubes or the gulf?

38 Passive Cigarette Smoke Exposure and Other Risk Factors for Invasive Pneumococcal Disease in Children: A Case-Control Study. Colleen S Chun, MD; Sheila Weinmann, MPH, PhD; Karen Riedlinger, MT, MPH; John P Mulloly, PhD

In a population-based, case-control study, 171 children, aged 0 to 12 years, with culture-confirmed invasive pneumococcal disease during the years 1994 to 2004 were identified. Two controls were matched to each case. The authors reviewed medical records of subjects and family members for information on household cigarette smoke exposure within 2 years of the diagnosis. Passive cigarette smoke exposure was not associated with invasive pneumococcal disease in this pediatric population.


A retrospective review of the Journal of the American Academy of Dermatology and the Archives of Dermatology was performed using the MEDLINE database for all original research articles published between 1970 and 2010. The frequency of research into acne vulgaris and rosacea decreased from 24% to 5.1%, psoriasis research increased from 17.6% to 26.5% (most likely because of the discovery of biologics), and skin cancer research increased from 4% to 48% (paralleling the increasing incidence of skin cancer).

49 Intervention to Reduce Inappropriate Ionized Calcium Ordering Practices: A Quality-Improvement Project. Darrell B Newman, MD; Konstantinos C Siontis, MD; Krishnaswamy Chandrasekaran, MD; Allan S Jaffe, MD; Deanne T Kashiyagi, MD

The authors hypothesized that most ionized calcium (iCa) tests are ordered for routine monitoring in asymptomatic patients and results do not influence clinical management. On retrospective review of clinical records they identified the first 100 consecutive patients admitted to the hospital internal medicine (HIM) services during January 2012 with an iCa test ordered during their hospitalization. An educational intervention regarding the appropriateness of iCa testing was undertaken targeting HIM clinicians. They then assessed the first 100 consecutive patients admitted to HIM services during November 2012. HIM services were responsible for 38% of iCa measurements before the educational intervention and 13% after, which represented a 66% reduction.

52 Temporal Comorbidity of Mental Disorder and Ulcerative Colitis. David Cawthorpe, PhD; Marta Davidson, MD

The authors used physician diagnoses from Calgary, Alberta, for patient visits from fiscal years 1994 to 2009 for treatment of any presenting concern (763,449 patients) to identify 5113 patients with a diagnosis of ulcerative colitis, and found 4192 patients also had a diagnosis of a mental disorder. Patients with mental disorder had a significantly higher annual prevalence. The mental disorder grouping neuroses/depression was most likely to arise before diagnosis of ulcerative colitis.

REVIEW ARTICLES

68 Acupuncture Safety in Patients Receiving Anticoagulants: A Systematic Review. Michael McCulloch, LAc, MPH, PhD; Arian Nachat, MD; Jonathan Schwartz; Vicki Casella-Gordon, RN, MS, CNS; Joseph Cook, JD

A search of PubMed, EMBASE, and Google Scholar revealed 39 citations of which 7 provided reporting quality sufficient to assess acupuncture safety in 384 anticoagulated patients (3974 treatments). Acupuncture appears to be safe in anticoagulated patients, assuming appropriate needling location and depth. The observed 0.003% complication rate is lower than the previously reported 12.3% following hip/knee replacement, and 6% following acupuncture in a prospective study of 229,230 all-type patients.

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74 An Idiosyncratic Reaction to Clopidogrel. Aaysha Kapila, MD; Lovely Chhabra, MD; Allison Diane Locke, MD; Pranav Patel, MD; Atul Khanna, MD; Chakradhar M Reddy, MD; Mark F Young, MD

Clopidogrel is an irreversible antiplatelet agent that antagonizes the adenosine diphosphate P2Y12 receptor on platelets disrupting fibrinogen—platelet complex formation. The authors report on a rare but clinically significant case of clopidogrel-induced hepatotoxicity in an elderly white woman.

77 Pemphigus Vulgaris with Tense Bullae. Emilie T Nguyen; Shinko K Lin, MD; Jasih J Wu, MD

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This report presents the case of a 37-year-old man with multiple Emergency Department visits for abdominal pain and with negative results for prior imaging studies, who was eventually diagnosed with intussusception after 5 years of recurrent symptoms. The case is followed by a review of the literature.

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CLINICAL MEDICINE
83 Image Diagnosis: Weber Syndrome: A Rare Presentation of Acute Leukemia—A Case Report and Review of the Literature. Vallappan Muthu, MD; Santosh Kumar, MD; Gaurav Prakash, DM; Prashant Sharma, MD; Subhash Varma, MD
For two weeks before presentation, a 13-year-old boy had fever, fatigue, and breathlessness, and painless lymphadenopathy on both sides of his neck, axilla, and groin. He developed drooping of the right upper eyelid. Non-contrast computed tomography scans of the head showed multiple hemorrhages.

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86 Harnessing the Affordable Care Act to Catalyze Delivery System Reform and Strengthen Emergency Care in America. John Maa, MD
As health care reform in the US evolves beyond insurance reform to encompass delivery-system reform, the opportunity arises to harness the Affordable Care Act to strengthen patient care in America. This article describes the innovations of the surgeon and acute care surgeon that have emerged to promote teamwork, to reduce readmissions, and to strengthen emergency care.

90 Agents for Change: Nonphysician Medical Providers and Health Care Quality. Nathan A Boucher, PA-C, MS, MPA, CPHQ; Marvin A McMillen, MD, FACS, MACP; James S Gould, PA-C, MS
Nonphysician medical providers may be the first caregivers to encounter the patient and can act as agents for change for an organization’s quality-improvement mandate by supporting best practices through the promotion of guidelines/protocols and playing active roles in patient engagement and organizational quality-improvement efforts.
ABSTRACT

Background: The objective of this study was to assess the financial implications of the continuity of care, for patients with high care needs, by examining the cost of government-funded health care services in British Columbia, Canada.

Methods: Using British Columbia Ministry of Health administrative databases for fiscal year 2010-2011 and generalized linear models, we estimated cost ratios for 10 cost-related predictor variables, including patients’ attachment to the practice. Patients were selected and divided into groups on the basis of their Resource Utilization Band (RUB) and placement in provincial registries for 8 chronic conditions (1,619,941 patients). The final dataset included all high- and very-high-care-needs patients in British Columbia (ie, RUB categories 4 and 5) in 1 or more of the 8 registries who met the screening criteria (222,779 patients).

Results: Of the 10 predictors, across 8 medical conditions and both RUBs, patients’ attachment to the practice had the strongest relationship to costs (correlations = -0.168 to -0.322). Higher attachment was associated with lower costs. Extrapolation of the findings indicated that an increase of 5% in the overall attachment level, for the selected high-care-needs patients, could have resulted in an estimated cost avoidance of $142 million Canadian for fiscal year 2010-2011.

Conclusions: Continuity of care, defined as a patient’s attachment to his/her primary care practice, can reduce health care costs over time and across chronic conditions. Health care policy makers may wish to consider creating opportunities for primary care physicians to increase the attachment that their high-care-needs patients have to their practices.

INTRODUCTION

The objective of this study was to assess the financial implications of continuity of care, for high-care-needs patients, by examining the cost of government-funded health care services in British Columbia (BC), Canada.

Continuity of Care

There is a consensus that continuity of care can improve the quality of patient care and a concomitant belief that continuity of care and care coordination can be cost-effective. Starfield and colleagues have pointed out that a discontinuity of primary care leads to patients seeking more specialist care, thereby increasing overall costs. However, empirical studies on the potential cost avoidance directly related to the continuity of primary care are few.

The cost-effectiveness of continuity of care has typically been inferred from its impacts on cost-related variables (eg, number of hospital admissions) but not directly on costs. For example, continuity of care has been associated with decreased hospital visits in the US and reduced ambulatory care-related hospitalizations in Canada. Conversely, lacking a primary care physician has been associated with an increased rate of hospital admissions, and in Ontario, Canada, patients without a regular family physician were 1.22 times more likely to visit an Emergency Department and 1.32 times more likely to have had a medical, nonelective hospital admission than were patients who reported having a regular family physician or general practitioner (GP).

In the conceptual framework of continuity of care described by Haggerty et al, three types of continuity of care were identified. Management continuity relates to the delivery of services by different care providers in a timely and complementary manner such that care is connected and coherent. Informational continuity refers to the extent to which information about past care is used to make current care appropriate to the patient. Finally, relational continuity refers to the therapeutic relationship between a patient and one or more providers that spans various health care events and results in an accumulated knowledge of the patient and care consistent with the individual’s needs. In our study, we used the concept of relational continuity between the patient and the primary care practice where the individual obtained most of his/her care, and operationalized it as the patient’s attachment to the main practice (see the section Attachment to Practice and Costs for a full definition).

Primary Care in British Columbia

British Columbia has funded, and continues to fund, family physicians primarily on a fee-for-service basis. GPs bill the BC Medical Services Plan, which is funded by the government. Reimbursement is rapid (most often within one month to six weeks), but is subject to a retrospective audit. There are also some sessional payments (usually blended with fee-for-service) provided for specific populations. BC has not adopted capitation payments for GPs except for a few small experiments. Salaried positions have not been offered for full-service GPs for many years. Conceptually, the BC model of primary care is very similar to the US concept of the patient-centered medical home.

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Canada’s most westerly province, BC has a population of approximately 4.4 million inhabitants. It is a multicultural province with representation from a variety of racial and ethnic groups. Approximately 50% of the population lives in the Vancouver and lower mainland areas. A large part of the province could be described as small town and rural and, in the north, even remote. This is true for many Canadian provinces. Canada’s population is about one-tenth that of the US, and BC’s population is approximately 13% of that of Canada. The median annual household income in BC in 2006 was Can$46,472 (Canadian dollars), and the average age of its citizens in 2011 was 41.9 years.10

Regarding GP income, the British Columbia Medical Association (now renamed Doctors of BC) indicates that in the 2011-2012 fiscal year (April 1, 2011, to March 31, 2012), the average income for all GPs was Can$199,512. To estimate income for regularly practicing GPs, Doctors of BC also uses a second estimate that excludes part-time GPs. For the 2011-2012 fiscal year, this cutoff point was Can$82,500. Thus, for GPs with incomes greater than Can$82,500, the average annual income, based on claims made to the BC Medical Service Plan, was Can$255,522. In accordance with the Canadian Constitution, the provision of health services is a provincial responsibility. Provincial and federal taxes are collected by the federal government, which provides health funding to the provinces through the Canada Health Transfer. Physician services and hospital services are single-payer, insured services, and, thus, residents of BC generally receive medical and hospital services without a charge or user fee. No other services are insured services and, thus, there is a complex set of rules regarding copayments for drugs, long-term care, and other allied health services.10

Primary care in BC is mainly provided by solo practitioners or small group practices. For payment and statistical purposes, individual physicians are identified by a practitioner number, and practices (corporations, sole proprietorships, etc) of one or more physicians are identified by a payee number (payments are made to the payee). Thus, for example, a GP operating as a solo practitioner would have 1 practitioner number and 1 payee number. In the 2010-2011 fiscal year there were 3397 practices (as defined by the payee number). Of this number, 1692 practices were composed of a single full-time or part-time GP. Only 524 (15.4%) of practices had more than 4 GPs.

Medical Services Plan payments are made on the basis of services provided in an extensive fee schedule. Generally, one service is provided during one visit. However, if the GP provides two unrelated services during one visit, the GP can bill for two services for that visit. Given how medical care is provided in BC, GPs, even in solo or small practices, can generally care for a range of patients, including those needing complex care. Incidence payments recently added to the fee schedule allow GPs to develop care plans and to take more time with their patients who have chronic or complex conditions.10

The BC Ministry of Health has developed a series of registries containing the records of people with chronic conditions. Patients in a given registry, such as diabetes, may have diabetes alone or may have diabetes plus other chronic conditions. In this article, we present findings based on data from eight different registries of chronic conditions. Thus, we have effectively conducted eight replications of our main finding, for patients with different chronic conditions.

Attachment to Practice and Costs

Hollander et al11 reported a clear inverse relationship between a patient’s attachment to a primary care practice and overall health care costs for hospital care, medical care, and the use of drugs. Those analyses were conducted for patients in BC with diabetes and congestive heart failure (CHF) at Resource Utilization Bands (RUB) categories 4 and 5 (hereafter referred to as RUB 4 and RUB 5, ie, high and very high-care-needs patients) using data for the 2007-2008 fiscal year. The RUBs are as defined in The Johns Hopkins Adjusted Clinical Groups Case-Mix System (described at www.healthpartners.com/files/57460.pdf).

The patient’s attachment to practice (defined as the percentage of services provided by the practice that provided the most services) was by far the strongest predictor of costs, and the relationship held after controlling for 9 other cost-related variables (eg, patient’s age, sex, geographic location). For these groups of patients, the stronger the patient’s attachment to practice, the lower the patient’s health care costs.

The inverse relationship between attachment and costs was found to be quite robust. In a number of additional analyses (not presented here, but available on request), we found that the inverse relationship between attachment and cost held up in the context of each of the other predictor variables we used in our analyses (eg, patient age, income, physician sex, physician place of graduation; see the Methods section). For example, when we looked at the relationship in the context of the patients’ age, we stratified the population into several age categories (eg, younger than 44 years, 45-64 years, 65-74 years, and 75 years and older) and found that even though the actual dollar amounts differed (eg, older patients had overall higher costs than younger patients), the inverse relationship between attachment and costs, which is the main focus of this article, held consistently. Similarly, we also found that the relationship held regardless of the number of chronic conditions the patient had.

The logic for focusing on attachment to a practice, rather than an individual GP, is as follows. If a patient has 12 services in a year and 9 of those services are from 1 practice, the patient’s attachment level would be 75% (9 of 12 services provided by the main practice). However, if the main GP in the practice provides 6 services and the other 3 services are provided by locum tenens or colleagues in the group practice whose billings go through the same payee number (ie, the payee number for that practice) the attachment level would be 50% (6 of 12 services). Given that the other services are provided on behalf of the main GP and not by other separate practices (drop-in clinics or GPs working in Emergency Departments), it was deemed that the most appropriate
indicator of continuity of care would be attachment to the practice of the main GP.

We postulate that continuity of care is inversely related to costs because of the regular and continuous relationship that develops between the GP and the patient. Through such a relationship, the GP is able to have a better understanding of the patient's health issues and life circumstances. Conversely, the patient trusts the GP and may reveal matters that may be of some tentative concern to him/her. This provides the GP and the patient the opportunity to anticipate and prevent or mitigate future health problems, which, in turn, can lead to a reduction in overall hospital days per year. This two-way interaction also means that GPs may not have to see patients as frequently compared with cases in which patients do not have a regular GP and instead go to drop-in clinics or Emergency Departments when they have a health concern. Thus, although the main cost reductions for patients with a high level of attachment are the result of their lowered use of hospital beds, these patients also use fewer GP services than do patients with low levels of attachment.11

In this study, we examined how attachment to practice, as a measure of continuity of care, directly affects total annual health care costs per patient for high-care-needs patients who have several different chronic conditions. Our goals were to replicate the findings of the study by Hollander et al11 for patients with diabetes and CHF with data from the 2010-2011 fiscal year, and expand the findings to patient groups with other chronic conditions.

**METHODS**

**Setting**

Data were extracted from the BC Ministry of Health's administrative databases for the 2010-2011 fiscal year. Access to the administrative data was obtained under a Ministry of Health Privacy Impact Assessment, which protects BC residents from unauthorized and/or inappropriate use of their private medical information and confirms that the analyses conducted will be done ethically and with respect for patient privacy.

**Patients**

The Ministry's databases contain data for all BC residents with a Medical Services Plan number, and for physicians and their billing practices. Because this study is in part a replication of the previous study,11 we used the same criteria to screen out patients who were atypical on the key predictor variables. Specifically, the inclusion criteria were:

- Adults age 18 years or older
- A minimum of 5 GP services
- RUB category 4 or 5 (the patient's overall health level likely affected their service usage and the costs of health care)
- Estimated not to have lived in a long-term-care facility in the 2010-2011 fiscal year
- Had not died in the 2010-2011 fiscal year
- Hospital costs that did not exceed Can$100,000. The rationale for this criterion was that hospital costs of more than Can$100,000 would indicate a patient who spent considerable time in hospital (eg, if the average hospital cost is Can$1000 per day, an annual cost of Can$100,000 implies a hospital stay of 100 days), but our study was about general practice and GPs caring for people living in the community. The number of patients excluded ranged from 7 to 29 per registry at RUB 4—or in percentages, fewer than 0.01% (diabetes) to 0.10% (stroke) of patients. There were 225 to 543 patients excluded at RUB 5, or between 0.76% (hypertension) and 2.25% (chronic kidney disease) of patients.
- Visits to 25 or fewer payees. This criterion was used in our previous study, but no patients were eliminated on the basis of this criterion in the present dataset.

These criteria and rationale are discussed more fully in the article by Hollander et al.11 We did, however, examine the distributions of all variables used in these analyses to ensure that the cutoff points for the inclusion criteria continued to be reasonable. As a result, we eliminated 22 patients whose costs through BC PharmaCare (a Ministry of Health assistance program for eligible prescription drugs and medical supplies) were atypical from the population as a whole (ie, greater than Can$100,000) because they skewed the data. No further adjustments of the various cutoff points were required. Only patients who met all of our inclusion criteria were retained for analysis. It should be noted that our dataset is not a sample; rather it contains the total population of British Columbians who met our selection criteria.

Patients in the following eight registries were analyzed: diabetes, CHF, chronic obstructive pulmonary disease (COPD), hypertension, angina, chronic kidney disease, osteoarthritis, and stroke.

**Design and Statistical Analyses**

The basic research question was to examine how a number of patient and practitioner variables influence health care costs. In this replication, we used 10 cost-related predictors. Five predictor variables related to patient characteristics: age, sex, residence location (4 categories of a “rurality index” defined for communities in BC12), median after-tax household income, and attachment to practice (the percentage of billable primary care services billed by the practice that billed for most of the patient’s services in 1 year). Five predictor variables related to the patient’s main GP’s characteristics: sex, length of time in family practice, full-time equivalent (FTE) status, number of physician payee numbers that the practitioner had (as a measure of the number of locations at which the physician practices), and whether the physician had graduated from medical school in Canada. The physician data were based on the physician in the practice who provided the most services to the patient. Separate analyses were conducted for patient groups defined by medical condition and RUBs 4 and 5.

The primary statistical analysis employed estimation of the generalized linear model with $\gamma$-distributed errors and the log link function, as recommended by Dunn et al10 for modeling mental health care costs. This model choice fits our data and purpose well. The $\gamma$-distribution is appropriate for dependent variables, such as costs, that are positive, continuous, and positively
skewed, and using the log link function produces incidence rate ratios as the model coefficients, which are easy to interpret and compare across predictors. Statistical analyses were conducted using Stata Version 11 (StataCorp, College Station, TX). Robust variance estimation was used for statistical hypothesis testing, and we report 95% confidence intervals for all generalized linear model estimates. We also report the bivariate associations of each predictor with the total cost, as a first-step assessment of the relationship that each predictor has with, and contributes to, the primary outcome variable.

**Primary Outcome Variable**

The primary outcome variable was the total, annual, per-patient, government-related health care cost for services provided. This included: costs of GP, diagnostic (laboratory tests, imaging, etc), and specialist services covered by the BC Medical Services Plan; pharmacy costs; and inpatient hospital costs.

**RESULTS**

Table 1 provides descriptions for patients in the replication study: diabetes and CHF at RUBs 4 and 5. The groups of patients for the other 6 conditions we studied (ie, angina, chronic kidney disease, COPD, hypertension, osteoarthritis, and stroke) were generally similar to patients with diabetes and CHF shown in Table 1. Details about these groups are provided in Table 2, available online at: www.thepermanentejournal.org/files/Winter2015/ChronicConditions.pdf.

The bivariate correlation coefficients between total cost and each predictor variable are shown in Table 3, in the columns for fiscal year 2010-2011. Of the 10 predictors examined, attachment to practice had the strongest relationship with the total cost in most groups, with higher attachment levels and higher household incomes associated with lower costs.

The pattern of relationships of the physician predictors with cost appears to be more consistent over time. Physician sex continued to have small to no impact on the cost across the four groups of patients. Physician place of graduation was a significant predictor of cost in three of the four groups, but no change was observed over the three-year period. Physician FTE factor, number of payee numbers, and to some degree years in practice showed stronger inverse relationships with cost in the more recent dataset.

The bivariate correlation coefficients between the predictors and costs for the remaining 6 chronic conditions studied are presented in Table 4. As was the case with diabetes and CHF, the patient’s attachment to practice had by far the strongest association with total cost, and this was consistent across all chronic conditions at both RUBs. The patient’s residence area, but not the patient’s sex, was associated with total costs at RUB 5 in most chronic conditions. As expected, patient age was related to cost in most groups, with higher costs associated with older patients with COPD, hypertension (RUB 4 only), angina, and osteoarthritis. However, this pattern reversed such that lower costs were associated with older patients in RUB 5 who had hypertension, chronic kidney disease, and stroke. The reasons for the latter finding are unclear in this context, but further explorations confirmed our main finding—the inverse

<table>
<thead>
<tr>
<th>Table 1. Description of patients in the 2010-2011 study¹</th>
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<tr>
<td>Demographic and cost variables</td>
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<tr>
<td>Age, years, mean (SD)</td>
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<tr>
<td>Male sex, %</td>
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<tr>
<td>Type of community, %</td>
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<td></td>
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<tr>
<td>Median family income, Can$, mean (SD)</td>
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<tr>
<td>Attachment to practice, %, mean (SD)</td>
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<tr>
<td>Cost variables (in Can$), mean (SD)</td>
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<tr>
<td>Medical Services Program</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Pharmacy costs²</td>
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<td></td>
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<tr>
<td>Hospital costs³</td>
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<td></td>
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<tr>
<td>Total costs</td>
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¹ Minimum age was set by inclusion criterion to 18 years.
² See reference 12 for definitions of the categories of communities in British Columbia.
³ Maximum hospital cost was set by inclusion criterion to Can$100,000.
⁴ Minimum value was set by inclusion criterion to 5 general practitioner services per year.
⁵ Maximum value was set by inclusion criterion to 25 payee numbers.

relationship between attachment and costs—was present in each age group. Of the physicians’ predictors, only the physician’s number of payee numbers and years in practice were consistently related to total costs across the conditions. The physician’s FTE factor and sex were also related to total costs in all but the chronic kidney disease groups.

The estimates for cost ratio obtained from the generalized linear model analyses, for all 8 chronic conditions at RUBs 4 and 5 from fiscal year 2010-2011, are presented in Figure 1A-H (available online at: www.thepermanentejournal.org/files/Winter2015/CostRatioEstimates.pdf). The cost ratio for a predictor indicates the percentage change in total cost (increase if it is > 1.0; decrease if < 1.0) per dollar spent, if that predictor is increased by 1 unit and holding all other predictors constant. For example, for patients in the diabetes RUB 4 group, a 1% increase in the patient’s attachment decreased the total cost by 1.2% (or by Can$0.012 per dollar spent) in 2010-2011 (all other variables held constant), whereas a 1-year increase in age increased the total cost by 0.50%, or Can$0.005 per dollar spent (all other variables held constant).

To summarize the results in Figure 1A-H, attachment to practice was the strongest predictor of total cost in each patient group. For patients with diabetes and CHF, a 1% increase in the patient’s attachment reduced the total cost by an estimated Can$1.20 to Can$1.58 per Can$100 dollars spent. Similarly for the other 6 chronic conditions, attachment to practice was consistently related to total cost, with a 1% increase in attachment being associated with Can$1.12 to Can$1.55 per Can$100 spent at RUB 4 and from Can$1.40 to Can$1.77 per Can$100 spent at RUB 5.

As for the other 9 predictors, 2 showed consistent results across patient groups. An increase in median household income was consistently associated with decreased costs, whereas the number of years the physician had been in practice was consistently not related to cost in all groups. The relationship of costs to the other predictors varied across the various diseases and RUB categories.

Using the cost ratio estimates from the generalized linear model analyses, we estimated the overall health care cost avoidance for a hypothetical situation in which all patients’ attachment to a primary care practice was increased by an average of 5%. The total hypothetical

Table 3. Bivariate correlations between total cost and each cost-related predictor variable in 2010-2011 and 2007-2008†

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<td>47,611</td>
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<td>26,463</td>
<td>22,557</td>
<td>20,052</td>
<td>17,123</td>
</tr>
<tr>
<td>Patient attachment</td>
<td>-0.196†</td>
<td>-0.179†</td>
<td>-1.62</td>
<td>(0.1052)</td>
<td>-0.299</td>
<td>(0.0444)</td>
</tr>
<tr>
<td>Patient age</td>
<td>0.033†</td>
<td>0.054†</td>
<td>0.009†</td>
<td>(NS)</td>
<td>0.019</td>
<td>(0.019)</td>
</tr>
<tr>
<td>Patient sex</td>
<td>0.022†</td>
<td>-0.040†</td>
<td>-0.006</td>
<td>(NS)</td>
<td>0.030†</td>
<td>(0.0001)</td>
</tr>
<tr>
<td>Patient residence</td>
<td>0.005†</td>
<td>-0.035†</td>
<td>-0.029†</td>
<td>(NS)</td>
<td>0.017</td>
<td>(0.0336)</td>
</tr>
<tr>
<td>Patient median income</td>
<td>-0.025†</td>
<td>-0.041†</td>
<td>-0.026†</td>
<td>(NS)</td>
<td>0.019</td>
<td>(0.019)</td>
</tr>
<tr>
<td>Physician sex</td>
<td>0.007†</td>
<td>0.004†</td>
<td>0.026†</td>
<td>(NS)</td>
<td>0.019</td>
<td>(0.019)</td>
</tr>
<tr>
<td>Physician place of graduation</td>
<td>0.014†</td>
<td>0.010†</td>
<td>0.023†</td>
<td>(NS)</td>
<td>0.019</td>
<td>(0.019)</td>
</tr>
<tr>
<td>Physician FTE factor</td>
<td>-0.043†</td>
<td>-0.024†</td>
<td>-0.088†</td>
<td>(NS)</td>
<td>-0.049</td>
<td>(NS)</td>
</tr>
<tr>
<td>Physician years in practice</td>
<td>-0.017†</td>
<td>-0.014†</td>
<td>0.047†</td>
<td>(NS)</td>
<td>-0.039</td>
<td>(NS)</td>
</tr>
<tr>
<td>Physician no. of payee numbers</td>
<td>0.054†</td>
<td>0.016†</td>
<td>0.119†</td>
<td>(NS)</td>
<td>0.086</td>
<td>(0.0198)</td>
</tr>
</tbody>
</table>

† The 2007-2008 correlations are from Hollander et al. Symbols are presented in place of the observed p values in some columns to make the table more readable, in the neo-Fishian framework; not as indicators of statistical significance of null hypothesis tests that the correlation coefficient equals zero. Boldface values indicate statistically significant differences across time.

* p value < 0.001.

0. British Columbia Ministry of Health, Primary Care Data Repository, Fiscal Years 2010-2011 and 2007-2008.


DOI: http://dx.doi.org/10.5735/086.046.0501.

FTE = full-time equivalent; NS = not significant (p > 0.05); RUB = Resource Utilization Band.
annual estimated cost avoidance would have been Can$142 million in the 2010-2011 fiscal year (Table 5). A 5% increase is a fairly modest goal and could be achieved if, in a practice, patients with lower attachment levels could be moved to higher attachment levels.

**DISCUSSION**

Within the continuity of care conceptual framework by Haggerty et al., our study provides an empirical investigation of the cost avoidance associated with the relational continuity of care. Of the 10 patient and physician variables related to health care costs, the patient’s attachment to a primary care practice, as a measure of the relational continuity of care, was the strongest and most consistent predictor of health care costs, and the inverse relationship held even after the effects of the other cost-related predictors were taken into account. A 1% increase in a patient’s attachment to practice decreased total health care costs by an estimated Can$1.12 to Can$1.77 per Can$100 spent for patients at RUBs 4 and 5 with a range of chronic diseases. Thus, one can conclude that our original findings were robust because they could be replicated over time and across a wider range of different chronic conditions.

The results of our study are limited by a number of factors related to working with administrative databases. First, although we tried to make reasonable assumptions with our inclusion criteria, how patients are entered and remain in the registries may vary across registries. Second, many patients have more than one chronic condition, and comorbidities have an impact on cost estimates. However, additional analyses conducted on the 2010-2011 data, identical to those described in the Introduction (not reported here but available from the authors), showed that the inverse relationship between costs and the patient’s attachment to a primary care practice holds consistently whether patients have one or multiple chronic conditions. In this context, we can also add that the inverse relationship held when we examined it separately in subgroups of men and women, different age groups, physician place of graduation, and the other predictor variables. Third, a more general limitation of our study is that the findings are based on databases from one Canadian province. Whereas the dollar amounts will vary, we believe that our main finding of the overall inverse relationship between attachment and cost would be replicated in other jurisdictions. Finally, our results are based on costs to government for medical and hospital services and pharmaceuticals only. The costs do not include health-related payments made by patients themselves or their insurers. Thus, this study focuses on costs to government. Data on private-pay costs for specific individuals were not available for analysis.

**Table 4. Bivariate correlation coefficients with total cost for patients with various chronic conditions and health care need level**

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>COPD</th>
<th>Hypertension</th>
<th>Angina</th>
<th>CKD</th>
<th>Osteoarthritis</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUB category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>23,360</td>
<td>16,528</td>
<td>64,350</td>
<td>27,752</td>
<td>16,729</td>
<td>58,919</td>
</tr>
<tr>
<td>Patient attachment to practice</td>
<td>0.0201*(NS)</td>
<td>-0.2919*(NS)</td>
<td>0.0638*(NS)</td>
<td>0.0247(NS)</td>
<td>0.0124(NS)</td>
<td>0.0117(NS)</td>
</tr>
<tr>
<td>Patient age category</td>
<td>0.0235*(NS)</td>
<td>-0.1766*(NS)</td>
<td>0.0235*(NS)</td>
<td>0.0279(NS)</td>
<td>0.0054(NS)</td>
<td>0.0011(NS)</td>
</tr>
<tr>
<td>Patient sex</td>
<td>0.0027(NS)</td>
<td>-0.0262(NS)</td>
<td>0.0019(NS)</td>
<td>0.0152(NS)</td>
<td>0.0014(NS)</td>
<td>0.0164(NS)</td>
</tr>
<tr>
<td>Patient residence area</td>
<td>-0.0219*(NS)</td>
<td>-0.0180*(NS)</td>
<td>-0.138*(NS)</td>
<td>0.0057(NS)</td>
<td>-0.0382*(NS)</td>
<td>0.0041(NS)</td>
</tr>
<tr>
<td>Patient median household income</td>
<td>-0.0264*(NS)</td>
<td>-0.0218*(NS)</td>
<td>-0.0295*(NS)</td>
<td>-0.0575*(NS)</td>
<td>-0.0257*(NS)</td>
<td>-0.0209*(NS)</td>
</tr>
<tr>
<td>Physician sex</td>
<td>0.0027(NS)</td>
<td>0.0564(NS)</td>
<td>0.0234(NS)</td>
<td>0.0018(NS)</td>
<td>0.0012(NS)</td>
<td>0.0081(NS)</td>
</tr>
<tr>
<td>Physician place of graduation</td>
<td>0.0042(NS)</td>
<td>0.0198(NS)</td>
<td>0.0253(NS)</td>
<td>-0.0029(NS)</td>
<td>0.0134(N)</td>
<td>0.00301(N)</td>
</tr>
<tr>
<td>Physician years in practice</td>
<td>-0.0541(NS)</td>
<td>-0.0369(NS)</td>
<td>-0.0767(NS)</td>
<td>-0.0343(NS)</td>
<td>-0.0578(NS)</td>
<td>-0.0317(NS)</td>
</tr>
<tr>
<td>Physician no. payee numbers</td>
<td>0.0705(N)</td>
<td>0.1443(N)</td>
<td>0.0476(N)</td>
<td>0.1102(N)</td>
<td>0.0421(N)</td>
<td>0.0729(N)</td>
</tr>
</tbody>
</table>

* Symbols are presented in place of the observed p values in some columns to make the table more readable, in the neoFisherian framework, not as indicators of statistical significance of null hypothesis tests that the correlation coefficient equals zero.

1. British Columbia Ministry of Health, Primary Care Data Repository, Fiscal Year 2010-2011.
DOI: http://dx.doi.org/10.5735/086.046.0501.

COPD = chronic obstructive pulmonary disease; CKD = chronic kidney disease; FTE = full-time equivalent; NS = not significant (p > 0.05); RUB = Resource Utilization Band.
Despite these limitations, our study is among the first that directly examines the impact that a patient’s attachment to his/her primary care practice has on the costs to the health care system. Another strength of our study is the practical definition of continuity of care, which we defined as attachment to practice and operationalized as the percentage of services a patient obtained from his/her most frequently visited primary care practice. As such, it is an empirically derived measure and not a subjective self-report of what a patient may think about their primary care physician. Even with the caveats noted in the preceding paragraph, we believe the relationship between attachment and cost is robust because the estimation models are based on population data, and we found the same results in different groups of high-needs patients with a wide variety of chronic conditions across all of BC.

CONCLUSION

We have shown that the continuity of care, defined as a patient’s attachment to his/her primary care practice, can reduce health care costs. We have replicated our previous findings and extended the results to other types of chronic illnesses. In all diseases we examined, increased attachment to a primary care practice was associated with lower costs, even when we controlled for a number of other cost-related variables, such as the patient’s age. Thus, health care policy makers may wish to consider creating opportunities for primary care physicians to increase the attachment that their patients with high-care needs have to their practices.

Our study has shown that even modest increases in attachment can have a substantial potential for cost avoidance. Regarding future cost-related analyses for higher-care-needs patients, researchers, evaluators, and planners should, on the basis of our findings, consider attachment to a primary care practice as a key driver of health care costs, along with age, sex, level of care need, and other such variables.  

 Disclosure Statement

Marcus Hollander, MA, MSc, PhD, and Helena Kadlec, MA, PhD, are with Hollander Analytical Services Ltd, Victoria, British Columbia. To ensure the independence and objectivity of evaluations conducted by Hollander Analytical Services, which are funded by the General Practice Services Committee, the British Columbia Ministry of Health and the Doctors of BC have signed an agreement, on behalf of the General Practice Services Committee, that guarantees the integrity, objectivity, and independence of any evaluations conducted by the General Practice Services Committee by Hollander Analytical Services. Thus, the author(s) have no conflicts of interest to disclose.

Acknowledgments

We acknowledge the funding provided for this research by the General Practice Services Committee, a partnership between the British Columbia Ministry of Health and the Doctors of BC. We would also like to acknowledge Angela Tessaro for her exceptional programming skills, ability to work with large administrative datasets, and setup of the datasets for our analyses. We thank Nicole Littlejohn for her assistance with preparing and submitting this article for publication. Finally, we would like to thank the anonymous reviewers of the manuscript for their helpful comments.

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

References

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Table 5. Estimated potential annual cost avoidance for a 5% increase in attachment to a primary care practice: all patients selected for analyses combined

<table>
<thead>
<tr>
<th>RUB category</th>
<th>n</th>
<th>Total health care costs in 2010-2011 (in Can$1M)</th>
<th>Estimated cost ratio per 1% increase in attachment [Exp(B)]</th>
<th>Estimated annual cost avoidance (in Can$1M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUB 4</td>
<td>148,646</td>
<td>859.0</td>
<td>0.9862</td>
<td>50.44</td>
</tr>
<tr>
<td>RUB 5</td>
<td>74,133</td>
<td>1185.5</td>
<td>0.9845</td>
<td>91.68</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>142.12</td>
</tr>
</tbody>
</table>

* Many patients appear in multiple registries.

* Computed as follows: 5 × (Exp(B) − 1) × (Total health care costs).
ORIGINALESEARCH & CONTRIBUTIONS

Efficacy and Utility of Phone Call Follow-up after Pediatric General Surgery versus Traditional Clinic Follow-up

Kevin Fischer, MSN, APRN; Virginia Hogan, MSN, APRN; Alesha Jager, MSN, APRN; Daniel von Allmen, MD

ABSTRACT

Context: Typical follow-up for surgical procedures consists of an interim history and brief focused physical examination. These appointments occupy clinic resources, require a time investment by the family, and rarely identify problems. Previous studies have demonstrated the safety of a postoperative phone call.

Objective: Compare a traditional in-person clinic postoperative visit with postoperative phone call follow-up regarding patient satisfaction, rate of successful follow-up, and clinical resource utilization in a large academic practice.

Design: A retrospective review of charts of patients who underwent select surgical procedures, along with a review of the clinic schedule for the same time period.

Main Outcome Measures: Efficacy, patient/family satisfaction, and impact on the clinic.

Methods: Families were contacted by telephone two weeks after select surgical procedures to assess for complications and questions. Cohorts of patients six months before and six months after implementation were assessed for main outcome measures.

Results: Before implementation, 55.5% of patients (427/769) who had one of the select surgical procedures were seen in the clinic postoperatively, and 62.6% (435/695) had a successful postoperative phone call follow-up. There were also 1090 overall scheduled postoperative appointments. Six months after implementation, overall postoperative appointments decreased 35.5% to 703. Overall, postoperative-scheduled visits decreased by 6% compared with new visits and other general follow-up visits, which each increased by 3%. A satisfaction survey revealed that 93% of patients (n = 231) were highly satisfied with the process. A hospital cost analysis suggested an 89% cost savings ($101.75 per patient for clinic visit vs $12.50 per patient for phone call follow-up).

Conclusion: Postoperative phone call follow-up is an effective tool that improves postoperative follow-up for the family, decreased use of clinic space and resources, and potential major cost savings for the institution.

INTRODUCTION

Postoperative follow-up of the patient who has undergone pediatric general surgery is important for ensuring and maintaining optimal patient outcomes. A postoperative phone call follow-up for select procedures offers potential advantages to the patient, family, and surgeon without sacrificing patient safety. The traditional postoperative visit after most general surgery procedures consists of an in-person clinic visit two to four weeks after the operation. Follow-up typically occurs in a defined clinic that requires the investment of substantial amounts of time by the family and the physician, requires hospital or practice resources to maintain and staff the clinic, and results in lost productivity at school and work for the family. In contrast, a postoperative phone call offers more efficient use of time and increased accessibility to

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Efficacy and Utility of Phone Call Follow-up after Pediatric General Surgery versus Traditional Clinic Follow-up

umbilical and inguinal hernia repair, simple lesion excision, circumcision, gastrectomus fistula closure, and central venous catheter placement.

Education of surgical faculty, surgery nurse practitioners (NPs), staff nurses who perform phone call follow-up, and surgery residents and fellows was provided before initiating the postoperative phone call protocol. Education included the specific surgical procedures to be included; educating parents and families about the follow-up process, including the option for a traditional in-person clinic postoperative visit; and entering a default order for a postoperative phone call in the electronic medical record (EMR) ordering system. The EMR was then used to create a work queue of patients due for a postoperative phone call.

Patients, or their parents depending on age, received a telephone call from an advanced practice nurse approximately two to three weeks after the date of surgery (Figure 1). At minimum, two attempts were made to contact each patient or his/her parent. The postoperative phone call included a detailed template of questions designed to identify complications or potential concerns requiring further evaluation. Data from the phone interview were incorporated into the EMR and became a permanent part of the patient’s record. The template questions covered general patient condition, assessment of surgical wound, level of pain, the need for and/or use of pain medications, activity level, diet intake, bowel and urinary function, and discussion of pathology results if indicated. The postoperative phone call also allowed parents to voice any other concerns or questions they may have had related to their child and his/her surgery. Last, the postoperative phone call gave the option for a clinic follow-up visit if the parent desired, and it encouraged the parent to call back with any questions or concerns.

When no one was reached, a voice message was left indicating that the surgery NP was calling to conduct the postoperative phone call. A second attempt to reach the parent by telephone was made the following day. All families received at least two calls on two different days of the week. Parents were able to call back at their leisure and speak with the NP to conduct the postoperative phone call.

Finally, for parents or patients who did not return the call or for those found to have telephone numbers that were disconnected or where it was not possible to leave voice messages, a detailed letter was mailed to the home. The letter indicated the Surgery Department’s attempts to call and conduct a postoperative phone call as well as contact numbers for the parent or patient to return the call.

For the purposes of the study, a successful traditional in-person, clinic postoperative visit was defined as the parent making an appointment and following through with the visit. A successful postoperative phone call was defined as successful family contact and completion of the questionnaire template.

RESULTS

We reviewed the clinic schedule for all patients coming to see the General Surgery Department from March 2011 through February 2012. In the 6 months before the implementation of the postoperative phone call follow-up, there were 1090 scheduled postoperative appointments made. Six months after implementation, the number of scheduled postoperative appointments was 703, or a 35.5% decrease. This created an overall change in the makeup of scheduled clinic appointments. There was a 6% decrease in all postoperative scheduled visits, from 27% to 21%. This increased the percentage of both new visits and other general follow-up visits by 3% each (Figure 2) during the same period.

A total of 1464 charts were reviewed of patients undergoing the selected

![Figure 1. Phone follow-up protocol. EMR = electronic medical record.](image1)

![Figure 2. Schedule clinic appointment by type.](image2)
procedures from the same period. We compared the rate of successful follow-up in clinic with postoperative phone calls. Before the postoperative phone call follow-up, 55.5% of patients (427/769) had a successful clinic follow-up after their surgical procedure. The number of patients who had a successful postoperative phone call for the same selected surgical procedures increased to 62.6% (435/695). A satisfaction survey was performed with families at the time they received their postoperative phone call from June 2012 to September 2012, with 93% (n = 231) reporting being satisfied with the process compared with making a clinic appointment.

The administrative cost of the telephone protocol was based on the average salary of an NP for time to complete the postoperative phone call. This cost was compared with the calculated fixed costs of running the clinic per patient, which is based on staffing and a proportionate share of other expenses for the clinic (supplies, purchased services, etc.). There was an 89% cost savings ($101.75 vs $12.50 per patient) for the institution when we performed a financial comparison looking at the decrease in administrative cost for the phone call follow-up (Table 1). The financial assessment did not account for the potential cost to the family of travel expenses or the lost time from work and school.

DISCUSSION

Telephone contact with patients has been demonstrated to be a useful tool in managing chronic illnesses, providing reassurance, monitoring disease status, and providing a means for questions and concerns to be addressed in the critical time for patients and families after surgery. A study in the adult population showed telephone communication after discharge assisted in recognizing and facilitating compliance in patients who required help in understanding their treatment plan and medications. This same study also reported significantly higher satisfaction rates among patients receiving postoperative phone calls vs the control group. A study conducted at the Arkansas Children’s Hospital, Little Rock, demonstrated the postoperative phone call as a safe means of postoperative follow-up. Although this study included many of the same surgeries our retrospective study addressed, it did not make or show direct comparisons of postoperative phone calls to actual traditional in-person clinic postoperative visits as related to the number of successful follow-ups between the 2 methods. Furthermore, the previous study included 3 pediatric surgeons and 563 patient charts. Our study was conducted on a much larger scale, with a substantially greater number of pediatric general surgeons involved and number of patient charts reviewed. Our protocol allows for taking advantage of the EMR to order, to track, and to record the follow-up process, making it possible to involve 19 pediatric general surgeons and 1464 patient charts over the study period. Incorporating the process into our standard work flow has created a sustainable process with minimal cost.

A Cochrane review of postoperative phone call follow-ups conducted by various health care professionals for patients discharged from the hospital found that postoperative phone calls made by hospital-based health professionals was considered a good means of information exchange for symptom management, patient instruction and education, provision of reassurance, and early recognition of potential complications. However, the review underscored the lack of methodologic quality of the reviewed studies. In addition, the effectiveness of postoperative phone calls compared with control groups was lacking, with no statistically significant differences demonstrated. Our current study clearly demonstrates the efficacy and utility of postoperative phone calls to achieve a significantly higher number of follow-ups compared with traditional in-person clinic postoperative visits. In addition, using postoperative phone calls as an alternative to the traditional in-person clinic postoperative visit allowed clinic time and space that would have otherwise been used for the postoperative visits to instead be available for new and other general follow-up surgical visits. This shift in clinic utilization is beneficial to the surgical practice without sacrificing patient satisfaction or safety.

A study in the Netherlands compared cost-effectiveness of clinic follow-up visits vs telephone follow-up after breast cancer surgery. A number of factors, including patient-related costs, loss of productivity, and hospital-level costs were evaluated. The study found hospital or clinic follow-up to be more costly overall vs postoperative phone call. Our study showed a substantial institutional financial savings of 88% when clinic follow-ups were replaced with telephone follow-ups for a specified number of surgical procedures. Although not directly measured in the study, a theoretical cost savings for the family may be extrapolated related to time saved from missed work and school, as well as travel time and expense.

There are several limitations of this study. First, the question of family satisfaction was asked at the end of the telephone follow-up call, which could cause possible bias. This could be addressed in a future study with a separate follow-up survey of families who could be reached, as well as those whom we were unable to reach for a postoperative telephone follow-up. Second, reviewing a full year for each method of follow-up could reduce any potential impact that school or family work schedules may have had on our rate of follow-up. It would have also been useful to track the average time of clinic visits compared with the average

### Table 1. Comparison of before and after implementation of telephone postoperative follow-up

<table>
<thead>
<tr>
<th>Measure</th>
<th>Before</th>
<th>After</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of scheduled postoperative clinic appointments</td>
<td>1090</td>
<td>703</td>
<td>36% decrease</td>
</tr>
<tr>
<td>Successful completion of follow-up (%)</td>
<td>56</td>
<td>63</td>
<td>p &lt; 0.01 ((\chi^2) test)</td>
</tr>
<tr>
<td>Cost (US $) per completed encounter: clinic vs phone</td>
<td>101.75</td>
<td>12.50</td>
<td>88% cost savings</td>
</tr>
</tbody>
</table>
time of postoperative calls. Finally, we did not track the number of patients and families we failed to reach via our postoperative phone call who later came to the Emergency Department or clinic for problems related to their surgical procedure.

CONCLUSION
Postoperative phone calls after select surgical procedures provide a higher rate of follow-up with patients and families compared with traditional in-person clinic postoperative visits. Along with an increased rate of follow-up, there was a noted decrease in direct cost to the institution and an inferred cost savings for families and patients. These were achieved with a high level of reported family satisfaction.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Acknowledgment
Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

References

Basic Facts
There is a side to human behavior in health and disease which is not a thing of the intellect, which is irrational and emotional but important. It is the mainspring of most of what we do and a great deal of what we think, but is in danger of being neglected by clinical science … How often, indeed, do we physicians omit to enquire about the basic facts of happiness and unhappiness in our patients’ lives. Yet all this is just as much the live fabric of medicine as biochemistry and applied physiology.

Elderly Patients with Glioblastoma Multiforme Treated with Concurrent Temozolomide and Standard- versus Abbreviated-Course Radiotherapy

Christine N Chang-Halpenny, MD; Jekwon Yeh, MD; Winston W Lien, MD

ABSTRACT

Context: Glioblastoma multiforme (GBM) is an aggressive neoplasm, with controversy regarding treatment in elderly patients.

Objective: To review outcomes of elderly patients aged ≥ 65 with newly diagnosed GBM treated with concurrent temozolomide and either standard-course radiotherapy (SRT) or abbreviated-course radiotherapy (ART).

Design: Retrospective review from 2003 to 2012.

Main Outcome Measure: Survival, comparing treatment regimens. One hundred patients received SRT (median dose = 60 Gy), and 29 received ART (median dose = 35 Gy). O6-methylguanine-DNA methyltransferase (MGMT) status was available for 26 SRT and 13 ART recipients.

Results: Median age was 70 years. Median follow-up was 11 months. At analysis, 3 patients were alive. Multivariate analysis of the entire cohort found SRT (hazard ratio [HR] = 0.421, p = 0.0001), Karnofsky Performance Score of 70 or higher (HR = 1.894, p = 0.0031), and more extensive surgery (HR = 0.466, p = 0.0023) were associated with longer survival time, but age was not. Median time to death with SRT was 13 months versus 5.4 months with ART, but the latter had worse prognostic factors, including lower Karnofsky Performance Scores, fewer gross total resections, and higher recursive partitioning analysis class. Recipients of SRT with methylated MGMT promoter had a trend toward longer survival compared with unmethylated MGMT (p = 0.06), but ART recipients had shorter survival with MGMT methylation (p = 0.02).

Conclusion: Elderly patients with multiple poor prognostic factors given ART had short survival times. Relative to other variables, MGMT status may not predict outcome for these patients.

INTRODUCTION

Glioblastoma multiforme (GBM) is a brain neoplasm with aggressive behavior and a 5-year overall survival less than 5%.1 At present, all treatment is essentially palliative, with eventual progression of disease. Current standard of care includes concurrent temozolomide (TMZ) and radiation therapy (RT) to 60 Gy in 2-Gy daily fractions, followed by adjuvant TMZ therapy.2-4 Optimal treatment of elderly patients is controversial because of their underrepresentation in early trials. This may be the result of multiple factors, including coexisting medical conditions and poor performance status. Studies before the TMZ era in elderly patients found improved survival with RT vs supportive care alone.5 Also, standard-dose and lower-total-dose irradiation were shown to have equivalent survival outcomes in elderly patients.6 A shorter course of RT may be more convenient for patients without being a detriment to survival.

Results of 2 recently published Phase 3 trials suggest that TMZ alone or RT alone may be good options in treating elderly patients with GBM and good Karnofsky Performance Scores, with similar outcomes from both arms.7,8 Both trials found that elderly patients with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation (mMGMT) had longer survival times than those with unmethylated MGMT (uMGMT) promoter when all were treated with TMZ alone.7,8 Previously, MGMT methylation has been shown to be associated with statistically significantly longer survival in patients receiving TMZ treatment.5,9 TMZ methylates DNA at multiple sites, including guanine at the O6 position, and unless repaired by a process with MGMT, the active drug leads to double-strand breaks. The efficacy of TMZ is thought to be related to MGMT methylation through increased drug sensitivity related to epigenetic gene silencing and enzyme inactivation. Despite this, it has not yet been widely incorporated into clinical practice (for prognosis or decision making).

Although these studies investigated outcomes from patients treated with single-modality TMZ or RT, the question remains whether concurrent TMZ with RT would be of further benefit to elderly patients. Results of existing studies looking at elderly patients given concurrent TMZ-RT suggest reasonable toxicities and a possible benefit of TMZ with RT; however, they are limited by either small numbers or lack of MGMT data,10-16 or are contradictory, with Niyazi et al17 finding that patients aged 70 years and older with lower Karnofsky Performance Scores might have worse outcomes if given TMZ. Results of a handful of studies also suggest that TMZ with an abbreviated course of RT or hypofractionated regimen may have similar outcomes as standard RT.18-21 Our study presents a review of our institution’s data of patients aged 65 years and older with newly diagnosed GBM who were treated with concurrent TMZ-RT, with standard-course RT.
Elderly Patients with Glioblastoma Multiforme Treated with Concurrent Temozolomide and Standard- versus Abbreviated-Course Radiotherapy

ORIGINAL RESEARCH & CONTRIBUTIONS

(RT) or abbreviated-course RT (ART). The latter typically is used for patients with worse prognostic factors. We also present MGMT data, available for a subset of our patients.

METHODS

Patients and Data Analysis

A retrospective review was conducted after obtaining permission from our institutional review board. We included patients aged 65 years or older treated with concurrent TMZ and RT for newly diagnosed GBM and treated at Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA. Patients’ clinical presentation (symptoms, neurologic status, Karnofsky Performance Score status), tumor characteristics (maximum tumor dimension and foci), degree of resection (according to the operative report), treatment, and outcomes were noted. The Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis status was determined via chart review.22,23 For patients aged 70 years and older, recursive partitioning analysis classification is limited to Classes IV, V, or VI, but Classes IV and V are differentiated only by working status. Because most of our patients were retirees, Classes IV and V were merged into 1 group for the purposes of the study. Survival time was calculated from date of tissue diagnosis to death (the latter via the US Social Security Death Index or the patient’s medical record). We did not note progression because of the retrospective nature of the study and variable imaging times.

Statistical analysis was conducted using GraphPad Prism 6.0 (GraphPad Software Inc, La Jolla, CA) and SAS (SAS Institute Inc, Cary, NC). Variables included in statistical analysis were radiation course, recursive partitioning analysis class, Karnofsky Performance Score (≤ 70 or > 70), tumor focality, extent of resection, up-front bevacizumab administration, and age. Survival times and significance were calculated using Kaplan-Meier analysis with univariate log-rank test and multivariate analysis with Cox proportional hazards model.

Table 1. Characteristics of patients receiving standard-course radiation therapy (RT) and abbreviated-course RT.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard course RT (n = 100)</th>
<th>Abbreviated course RT (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>69 (65-93)</td>
<td>75 (66-87)</td>
</tr>
<tr>
<td>Men</td>
<td>64</td>
<td>62</td>
</tr>
<tr>
<td>Women</td>
<td>36</td>
<td>38</td>
</tr>
<tr>
<td>Seizures</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>Headache</td>
<td>31</td>
<td>34</td>
</tr>
<tr>
<td>Vision changes</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Motor deficits</td>
<td>28</td>
<td>45</td>
</tr>
<tr>
<td>Numbness</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>38</td>
<td>41</td>
</tr>
<tr>
<td>RTOG RPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Classes IV, V</td>
<td>94</td>
<td>66</td>
</tr>
<tr>
<td>Class VI</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>Karnofsky Performance Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Score (range)</td>
<td>90 (50-100)</td>
<td>70 (30-90)</td>
</tr>
<tr>
<td>Tumor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum size, cm (range)</td>
<td>4.3 (1.2-8)</td>
<td>5 (2-8)</td>
</tr>
<tr>
<td>Unifocal</td>
<td>81</td>
<td>72</td>
</tr>
<tr>
<td>Multifocal</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>29</td>
<td>31</td>
</tr>
<tr>
<td>Subtotal resection</td>
<td>41</td>
<td>62</td>
</tr>
<tr>
<td>Gross total resection</td>
<td>30</td>
<td>7</td>
</tr>
<tr>
<td>Median RT dose, Gy (range)</td>
<td>60 (50.4-64.08)</td>
<td>35 (20-42)</td>
</tr>
<tr>
<td>Carmustine wafers</td>
<td>6</td>
<td>3.4 (1/29)</td>
</tr>
<tr>
<td>Concurrent bevacizumab</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>MGMT status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Available (no.)</td>
<td>26 (26/100)</td>
<td>45 (13/29)</td>
</tr>
<tr>
<td>Unmethylated (no.)</td>
<td>73 (19/26)</td>
<td>54 (7/13)</td>
</tr>
<tr>
<td>Methylated (no.)</td>
<td>27 (7/26)</td>
<td>46 (6/13)</td>
</tr>
</tbody>
</table>

* Data are in percentage of patients unless indicated otherwise.

MGMT = O6-methylguanine-DNA methyltransferase; RTOG RPA = Radiation Therapy Oncology Group recursive partitioning analysis.

RESULTS

All Patients

From 2003 to 2012, we identified 129 patients who were age 65 years or older with newly diagnosed, histologically proven GBM. Of these, 100 patients were treated with SRT and 29 patients with ART. Promoter hypermethylation data for MGMT, via methylation-specific polymerase chain reaction, was available for 30% of patients. Overall median age was 70 years (range = 65 to 93 years), and median follow-up time was 11 months (range = 17 to 71.8 months).

The most common presenting symptoms were altered mental status (38.8%), followed by headache and change in motor function (both 31.8%), seizures (22.5%), changes in vision (13.2%), and sensory changes (7.8%). Gross total resection was performed in 24.8% of patients; subtotal resection, in
Elderly Patients with Glioblastoma Multiforme Treated with Concurrent Temozolomide and Standard-versus Abbreviated-Course Radiotherapy

45.7%; and biopsy only, in 29.5%. Median overall survival was 10.5 months (range = 1.7 to 57.9 months). By the time of retrospective analysis, only 3 patients were still alive (overall mortality of 98.4%, Figure 1), all having received SRT. As expected, the group that received ART had worse prognostic factors (see Abbreviated-Course Radiation Therapy section). Otherwise, the groups were relatively similar in clinical characteristics (Table 1).

Kaplan-Meier analysis with the log-rank test showed statistically significantly higher median survival time with SRT (p < 0.0001). In addition, the log-rank test showed higher median survival times for recursive partitioning analysis Class IV/V compared with Class VI (p = 0.0413), as well as for those with Karnofsky Performance Scores above 70 (p = 0.0013), those who underwent resection rather than biopsy (p = 0.0007), and those patients not given bevacizumab (with TMZ) as initial treatment (p = 0.0003). The MGMT status was not significant on log-rank for the entire cohort, but it became a significant factor when tested separately in the SRT and ART groups. When these variables, as well as age, were included in multivariate analysis, only RT course (SRT hazard ratio [HR] = 0.421, p = 0.0001), Karnofsky Performance Score ≤ 70 HR = 1.894, p = 0.0311, and resection rather than biopsy (gross total resection: HR = 0.466, p = 0.0023; subtotal resection: HR = 0.455, p = 0.0003) were significant according to the Cox proportional hazards model. Age was not a significant factor. The median survival time for patients with Karnofsky Performance Scores above 70 was 13 months vs 7.4 months for those with scores of 70 or below. The median survival time for patients who underwent biopsy was 6.13 months vs 13.3 months for those who underwent subtotal resection and 14 months for patients who underwent gross total resection. More complete data regarding RT course and MGMT data are reported separately as below.

**Standard-Course Radiation Therapy**

The median age of patients treated with SRT was 69 years (range = 65 to 93 years). Most patients received 60 Gy in 30 fractions (range = 50.4 to 64.08 Gy). All but 1 patient received partial brain irradiation. In addition to TMZ, 16% received bevacizumab as part of initial therapy, and 6 patients had carmustine wafers implanted at the time of surgery. The median time to death was 13 months (range = 2 to 72 months). Salvage (rescue) chemotherapy was given to 56% of SRT recipients. Four patients received repeated irradiation to treat a recurrence. The median time from salvage therapy to death for SRT recipients was 7.3 months (range = 0.3 to 30 months). Overall survival at 1 year was 54% and at 2 years was 17%. See Table 2 for outcomes data comparing SRT and ART.

On univariate analysis, the median survival time was significantly longer for patients not given bevacizumab as part of initial treatment (p = 0.0216) and for patients who received gross total resection or subtotal resection vs biopsy (p = 0.0024). On multivariate analysis, both bevacizumab (HR = 1.896, p = 0.0268) and degree of resection (gross total resection: HR = 0.451, p = 0.003; subtotal resection: HR = 0.481, p = 0.0033) remained significant variables affecting

**Table 2. Patient salvage treatment and outcomes by radiation therapy (RT) course**

<table>
<thead>
<tr>
<th>Salvage therapy</th>
<th>Standard-course RT (n = 100)</th>
<th>Abbreviated-course RT (n = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received repeated irradiation, %</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Received chemotherapy, %</td>
<td>56</td>
<td>24</td>
</tr>
<tr>
<td>Median months from diagnosis to salvage therapy (range)</td>
<td>9.5 (2.3-60.7)</td>
<td>7.2 (2.3-21.8)</td>
</tr>
<tr>
<td>Median months after salvage therapy to death (range)</td>
<td>7.3 (0.3-30)</td>
<td>6.6 (1.4-9.7)</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median follow-up, months (range)</td>
<td>13 (2-71.8)</td>
<td>5.4 (1.7-29.9)</td>
</tr>
<tr>
<td>Overall mortality, %</td>
<td>97</td>
<td>100</td>
</tr>
<tr>
<td>Median months from surgery to death (range)</td>
<td>13 (2.71)</td>
<td>5.4 (1.7-30)</td>
</tr>
<tr>
<td>Overall survival at 1 year, %</td>
<td>54</td>
<td>8</td>
</tr>
<tr>
<td>Overall survival at 2 years, %</td>
<td>17</td>
<td>1</td>
</tr>
</tbody>
</table>
survival times. Of note, in the SRT cohort, those patients given bevacizumab had significantly worse Karnofsky Performance Scores (≤ 70 for 12 patients and > 70 for 6 patients, \( p = 0.0733 \)), which may be a confounding factor.

**Abbreviated-Course Radiation Therapy**

The median age for patients treated with ART was 75 years (range = 66 to 87 years). Compared with patients treated with SRT, recipients of ART had lower Karnofsky Performance Scores (≤ 70 for 51% vs > 70 for 18%, \( p = 0.0002 \)), fewer gross total resections (7% vs 30%, \( p = 0.011 \)) and higher recursive partitioning analysis (Class VI/V 87.6% vs Class V 12.4%, \( p = 0.0003 \)). Most patients received 35 Gy in 10 daily fractions (range = 20 to 42 Gy). Field of treatment consisted of partial-brain irradiation for 59% of patients, whereas 41% received whole-brain irradiation. The median time to death was 5.4 months (range = 1.7 to 30 months). More ART recipients received concurrent bevacizumab as first-line treatment (16% vs 31%, \( p = 0.07 \)) compared with those in the SRT group. One patient had carmustine wafers implanted. Only 24% received salvage chemotherapy, and none received repeated irradiation. Median time from salvage to death for ART patients was 6.6 months (range = 1.4 to 9.7 months). Overall survival at 1 year was 8% and at 2 years was merely 1%.

By univariate analysis, median survival time was significantly longer for patients with Karnofsky Performance Scores above 70 (\( p = 0.0073 \)), unmethylated 06-methylguanine-DNA methyltransferase (\( p = 0.0021 \)), and unfocal disease (\( p = 0.0026 \)). The extent of resection and bevacizumab treatment were not significant variables, in contrast to the SRT group. After multivariate analysis, only Karnofsky Performance Score (≤ 70: HR = 3.312, \( p = 0.0074 \)) and tumor focality (multifocality: HR = 4.259, \( p = 0.0031 \)) were significant.

**06-Methylguanine-DNA Methyltransferase Promotor Status**

Data on MGMT were available for 39 patients (26 SRT and 13 ART). Log-rank analysis of MGMT status for all patients did not show significantly different survival times (\( p = 0.5412 \)). However, methylation status was significantly associated with outcomes for patients when data were analyzed separated by the RT course given. For patients whose MGMT status was known, the SRT group had more gross total resections compared with those in the ART group (\( p = 0.0272 \)), more cases of recursive partitioning analysis Class VI (\( p = 0.0620 \)), and more patients treated with bevacizumab up front (\( p = 0.0597 \)). Median age was similar, and Karnofsky Performance Score was slightly lower (median Karnofsky Performance Score = 90 for ART vs 80 for SRT). Of the 26 SRT patients for whom MGMT data were known, 7 had unmethylated status and 19 had methylated status. Patients given SRT with methylated status had a trend toward longer survival times compared with those with unmethylated status: 28.4 months (range = 3.4 to 57.9 months) vs 10.3 months (range = 3.5 to 49.7 months, \( p = 0.0602 \), Figure 2). Median age was slightly higher in the SRT group for patients with methylated status than for those with unmethylated status (75 vs 69 years); otherwise, there were no significant differences by recursive partitioning analysis class, Karnofsky Performance Score, surgery type, or radiation dose.

Of the 13 ART patients with MGMT data, 6 had methylated and 7 had unmethylated status. Paradoxically, patients treated with ART actually had significantly shorter survival if promoter methylation was present. Time to death for patients with methylated status was 3 months (range = 1.7 to 8.6 months) vs 14.5 months (range = 2.2 to 14.5 months) for those with unmethylated status (\( p = 0.021 \)). In the ART group, patients with methylated status did not differ significantly from those with unmethylated status in potential prognostic factors.

**DISCUSSION**

Recent large randomized trials have investigated outcomes for elderly patients with newly diagnosed GBM treated with TMZ alone or RT alone, but not combined. Current guidelines for GBM management from the National Comprehensive Cancer Network have treatment arms stratified by performance status but have a range of options for patients over age 70 years who have Karnofsky Performance Scores of 70 or higher; these options include either concurrent ART = abbreviated-course radiation therapy; mMGMT = methylated 06-methylguanine-DNA methyltransferase; SRT = standard-course radiation therapy; uMGMT = unmethylated 06-methylguanine-DNA methyltransferase.
treatment with TMZ-RT, hypofractionated RT alone, or TMZ therapy alone (if MGMT promoter is methylated). Barker et al. looked at 291 patients aged 65 years and older who were treated with RT with or without chemotherapy and found that 2-year overall survival was significantly improved with TMZ: 14% vs 41%. Findings of other retrospective studies of elderly patients given combined-modality therapy suggest good tolerance of treatment. 

According to our study of elderly patients with a range of Karnofsky Performance Scores, concurrent therapy with TMZ and standard-dose RT appeared to offer reasonable survival outcomes, with a median survival time of 13 months. Patients with multiple poor prognostic factors given ART had shorter survival times, with a median survival of 5.4 months. Multivariate analysis of prognostic factors suggested that SRT, Karnofsky Performance Score above 70, and more extensive resection are associated with better survival outcomes. For patients who received SRT, treatment with bevacizumab was associated with a shorter time to death, possibly confounded by SRT recipients given bevacizumab having lower Karnofsky Performance Scores to begin with. In both RTOG0825 and AVAglio, the addition of bevacizumab to treatment with TMZ and radiation found no significant difference in the duration of overall survival between bevacizumab and placebo, although progression free survival was improved with bevacizumab in the latter study. 

Bevacizumab was not a significant variable on multivariate survival analysis for the entire cohort but may be a relevant area of study to further investigate its impact on older patients with GBM. Our study is limited by its retrospective nature, treatment by multiple providers, and the small number of patients for whom MGMT data are available.

Before TMZ was introduced, an abbreviated course of RT with a smaller dose of total radiation was suggested as treatment of GBM in elderly patients. Keime-Guibert found that compared with supportive care alone, RT (50 Gy) modestly improved survival without reducing quality of life or cognition in elderly patients with high-grade gliomas and good Karnofsky Performance Scores. Rao et al. looked at elderly patients with Karnofsky Performance Scores of 50 or higher given a standard course of RT (60 Gy in 30 fractions) vs short-course irradiation (40 Gy in 15 fractions) and found decreased corticosteroid use and no significant difference in survival. In the trial by Stupp et al., 30% of patients were age 60 to 70 years. In this subset of patients, median survival was similar to or slightly better for patients receiving RT alone vs chemoradiation therapy. Although patients treated with TMZ had better overall survival over time because of a small subset of surviving patients. In the 2 largest Phase 3 trials focusing specifically on elderly patients (age 65 years or older), single-modality TMZ and RT each appears equally efficacious. The German Cancer Society Neuro-Oncology Working Group found that dose-dense TMZ was not inferior to standard-dose RT, and health-related quality-of-life surveys were similar for both groups. The Nordic Clinic Brain Tumour Study group looked at single-modality treatment with TMZ, standard-dose RT, or hypofractionated RT regimen. TMZ treatment alone had significantly better survival outcomes compared with standard RT but was equal to treatment with hypofractionated radiation. There was a trend for patients over age 70 years to have improved survival with TMZ treatment alone. In both studies, patients with mMGMT (vs uMGMT) promoter who were treated with TMZ had significantly improved survival. Given concerns about the ability of elderly patients to tolerate concurrent treatment, neither study looked at concurrent chemoradiation therapy and thus did not provide data on how methylation status affects patients given both TMZ and RT.

In our study, mMGMT status appeared beneficial for patients treated with SRT, although it probably did not reach statistical significance because of small numbers of patients. Interestingly, this was not true for patients treated with ART, in which patients with uMGMT status actually had better survival rates. It seems unlikely that methylation would be related to worse prognosis in these patients; rather, it is more likely that given the multiple poor prognostic factors and lower radiation dose in these patients, MGMT status may be less predictive compared with other prognostic factors when concurrent treatment with TMZ and RT is given. When we compared the two groups that had MGMT data, ART recipients had significantly fewer gross total resections, and there were more patients with recursive partitioning analysis Class VI, although this was not statistically significant.

Given the length of standard-dose RT, hypofractionation or an abbreviated course of RT is attractive for patient convenience and comfort, possibly with as few as 6 fractions of treatment. Pilot and Phase 2 studies looking at hypofractionated courses of RT with TMZ have typically excluded elderly patients, but they show similar outcomes compared with SRT. Hypofractionation studies that included elderly patients lack MGMT data but suggest similar outcomes with hypofractionated courses compared with standard RT. Further studies on hypofractionation and concurrent and adjuvant TMZ therapy in elderly patients with good prognostic factors will, we hope, shed more light on the interplay of MGMT status and concurrent treatment for this subset of patients.

CONCLUSION

In our study, patients aged 65 years and older with newly diagnosed GBM had good outcomes when treated with SRT and concurrent TMZ, whereas patients with poor prognostic factors treated with ART and TMZ had shorter survival times. Methylated MGMT promoter status trended toward longer survival in SRT recipients, but may not be as useful in predicting outcomes for patients with worse prognostic factors treated with ART. Further investigation of the effect of bevacizumab on older patients with GBM is warranted. In the future, stratifying patients by MGMT status, as well as prognostic factors, and adapting treatment (with consideration of hypofractionated radiation regimen) on the basis of these factors would probably offer patients a better balance of treatment while minimizing toxicity.
Disclosure Statement
The author(s) have no conflicts of interest to disclose.

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We would like to thank Richard M Green, MD, for his assistance.
Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

References
This photograph was taken during a visit to Claude Monet’s famous gardens and home in the town of Giverny, in the Normandy region of northern France.

Dr. Munz is the Chief of Ophthalmology for the Orange County Medical Center and Regional Chief of Ophthalmology for the Southern California Permanente Medical Group.
Risk Factors for Neck Hematoma after Thyroid or Parathyroid Surgery: Ten-Year Analysis of the Nationwide Inpatient Sample Database

Ahmed Dehal, MD, MPH; Ali Abbas, MD, MPH; Farabi Hussain, MD; Samir Johna, MD

ABSTRACT

Context: Postoperative neck hematoma is a well-known complication of thyroid and parathyroid surgery. Better understanding of risk factors for hematoma formation will help define high-risk populations.

Objective: To examine possible risk factors for neck hematoma after thyroid or parathyroid surgery.

Design: Retrospective analysis of hospital discharge data from the Nationwide Inpatient Sample database.

Methods: Using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis and procedures codes, we identified adults who underwent thyroid or parathyroid surgery and in whom neck hematoma subsequently developed. Information about demographic, clinical, and hospital characteristics was collected. Multivariate regression analyses were used to predict independent risk factors for neck hematoma.

Results: We identified 147,344 thyroid and parathyroid operations performed nationwide between 2000 and 2009. Overall incidence of postoperative neck hematoma was 1.5% (n = 2210). In multivariate analysis, age 65 years and older (odds ratio [OR] = 1.8, 95% confidence interval [CI] = 1.4-2.1), male sex (OR = 1.3, 95% CI = 1.2-1.4), African-American race (OR = 1.5, 95% CI = 1.2-1.7), being from the South (OR = 1.3, 95% CI = 1.1-1.4), comorbidity score of 3 or more (OR = 2, 95% CI = 1.6-2.6), history of alcohol abuse (OR = 2.7, 95% CI = 1.6-2.5), Graves disease (OR = 3, 95% CI = 2.1-4.1), and subternal thyroidectomy (OR = 3.3, 95% CI = 2.8-3.9) were associated with a higher risk of neck hematoma.

Conclusion: We identified demographic and clinical factors associated with increased risk of neck hematoma after thyroid or parathyroid surgery.

INTRODUCTION

Postoperative hemorrhage is a well-known complication of thyroid and parathyroid surgery and can be life-threatening because of acute airway obstruction. Because close observation, early detection, and airway management are keys to managing this complication, the risk of postoperative hemorrhage may be a limiting factor for outpatient thyroid surgery or early discharge from the hospital.1-3

Previous research has shown that certain patient demographics (age and sex), underlying thyroid pathology (malignant histology), and extent of resection (total vs partial thyroidectomy) are associated with an increased risk of postoperative hemorrhage.4-6

Although these subgroups have been identified empirically to be at greater risk of postoperative bleeding complications, there is little evidence from large-scale nationwide studies to support this notion. The rarity of neck hematoma has been a challenge in evaluating the factors associated with it.

A better understanding of risk factors for hematoma formation will help in identifying those who are at risk of this complication. The objective of this study was, using a nationwide database, to identify risk factors for the development of neck hematoma after thyroid or parathyroid surgery.

METHODS

Study Design and Data Source

This is a retrospective analysis of hospital discharge data from the Nationwide Inpatient Sample (NIS) database between 2000 and 2009. The NIS database is a component of the Healthcare Cost and Utilization Project (HCUP), sponsored by the Agency for Healthcare and Quality. This database represents the largest inpatient database in the US. The NIS represents 20% stratified random sampling of US hospitals. The database contains data from 1050 hospitals with more than 38 million discharges annually from a variable number of states, ranging from 8 in 1988 to 44 in 2009. Detailed information on the NIS design can be found online. The NIS database has been used previously in studies addressing various questions across the spectrum of medical specialties, including several studies on thyroid and parathyroid surgery.8

We used the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis and procedures codes to identify adult patients who underwent thyroid and parathyroid surgery for treatment of thyroid and parathyroid diseases in whom neck hematoma (Codes 998.11 and 998.12) developed postoperatively during the same hospitalization. Primary ICD-9-CM diagnosis and procedure codes are shown in the Sidebars: ICD-9-CM Diagnosis Codes and ICD-9-CM Procedure Codes. Because

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Samir Johna, MD, is a General Surgeon at the Fontana Medical Center in CA. E-mail: samir.d.johna@kp.org.
Table 1. Patient and hospital characteristics by neck hematoma status (yes/no), Nationwide Inpatient Sample 2000-2009, N = 147,334

<table>
<thead>
<tr>
<th>Variable</th>
<th>Yes (n = 2210) Number (%)</th>
<th>No (n = 145,134) Number (%)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
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<td>Age at discharge, years</td>
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<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>18-40</td>
<td>339 (15.3)</td>
<td>31,683 (21.9)</td>
<td></td>
</tr>
<tr>
<td>41-65</td>
<td>1137 (51.4)</td>
<td>77,403 (53.3)</td>
<td></td>
</tr>
<tr>
<td>&gt; 65</td>
<td>734 (33.2)</td>
<td>36,048 (24.8)</td>
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<td>Sex</td>
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<tr>
<td>Male</td>
<td>708 (32.1)</td>
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</tr>
<tr>
<td>Female</td>
<td>1498 (67.9)</td>
<td>112,653 (78.2)</td>
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<td>Raceb</td>
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</tr>
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<td>White</td>
<td>1054 (47.7)</td>
<td>78,001 (53.7)</td>
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<td>African American</td>
<td>351 (15.9)</td>
<td>15,622 (10.8)</td>
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<td>115 (5.2)</td>
<td>9688 (6.7)</td>
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<tr>
<td>Asian</td>
<td>66 (3.0)</td>
<td>4385 (3.0)</td>
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<td>Insurance typec</td>
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<td></td>
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<tr>
<td>Medicare</td>
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<td>43,380 (29.9)</td>
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<td>Medicaid</td>
<td>176 (8.0)</td>
<td>9711 (6.7)</td>
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<td>Self-pay</td>
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<td>Residential incomed</td>
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<td>24,354 (17.1)</td>
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<td>2</td>
<td>534 (24.7)</td>
<td>31,769 (22.4)</td>
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<td>3</td>
<td>548 (25.4)</td>
<td>35,293 (24.8)</td>
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<td>4</td>
<td>598 (27.7)</td>
<td>50,724 (35.7)</td>
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</tr>
<tr>
<td>Year of discharge</td>
<td></td>
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<td>&lt; 0.001</td>
</tr>
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<td>2000-2002</td>
<td>533 (24.1)</td>
<td>40,493 (27.9)</td>
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<tr>
<td>2003-2006</td>
<td>919 (41.6)</td>
<td>60,889 (42.0)</td>
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<td>2007-2009</td>
<td>758 (34.3)</td>
<td>43,752 (30.1)</td>
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</tr>
<tr>
<td>West</td>
<td>432 (19.5)</td>
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<tr>
<td>South</td>
<td>860 (38.9)</td>
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<td>Northeast</td>
<td>426 (19.3)</td>
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<tr>
<td>Midwest</td>
<td>492 (22.3)</td>
<td>29,308 (19.5)</td>
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<td>0</td>
<td>892 (40.4)</td>
<td>73,875 (50.8)</td>
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<td>1</td>
<td>342 (15.5)</td>
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<td>2</td>
<td>508 (23.0)</td>
<td>32,173 (22.2)</td>
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<td>≥ 3</td>
<td>468 (21.2)</td>
<td>19,854 (13.7)</td>
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<td>Obesity</td>
<td></td>
<td></td>
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<tr>
<td>Nonobese</td>
<td>2064 (93.4)</td>
<td>135,713 (93.5)</td>
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<td>Obese</td>
<td>146 (6.6)</td>
<td>9421 (6.5)</td>
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<td>Smoking status</td>
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<td>Nonsmoker</td>
<td>1878 (85.0)</td>
<td>127,322 (87.7)</td>
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<tr>
<td>Smoker</td>
<td>332 (15.0)</td>
<td>17,812 (12.3)</td>
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<tr>
<td>Alcohol abuse</td>
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</tr>
<tr>
<td>No</td>
<td>2183 (98.8)</td>
<td>144,617 (99.6)</td>
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</tr>
<tr>
<td>Yes</td>
<td>27 (1.2)</td>
<td>517 (0.4)</td>
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<td>Hospital bed size</td>
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<tr>
<td>Small</td>
<td>210 (9.5)</td>
<td>14,723 (10.2)</td>
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<tr>
<td>Medium</td>
<td>503 (22.8)</td>
<td>33,176 (22.9)</td>
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<tr>
<td>Large</td>
<td>1489 (67.6)</td>
<td>96,894 (66.9)</td>
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<td>Location of hospital</td>
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<tr>
<td>Rural</td>
<td>147 (6.7)</td>
<td>9991 (6.9)</td>
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<td>Urban</td>
<td>2055 (93.3)</td>
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<td>Teaching status of hospital</td>
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<td>Nonteaching</td>
<td>891 (40.5)</td>
<td>61,131 (42.2)</td>
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<td>Teaching</td>
<td>1311 (59.5)</td>
<td>83,662 (57.8)</td>
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<td>Hospital volume</td>
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<td>Low</td>
<td>501 (22.7)</td>
<td>30,053 (20.7)</td>
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<tr>
<td>High</td>
<td>1709 (77.3)</td>
<td>115,081 (79.3)</td>
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<tr>
<td>Diagnosis</td>
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<td>&lt; 0.001</td>
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<tr>
<td>Parathyroid diseases</td>
<td>386 (17.5)</td>
<td>26,116 (18.0)</td>
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<tr>
<td>Benign thyroid disease</td>
<td>1172 (53.0)</td>
<td>78,288 (53.9)</td>
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</tr>
<tr>
<td>Thyroid cancer</td>
<td>530 (24.0)</td>
<td>36,508 (25.2)</td>
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</tr>
<tr>
<td>Graves disease</td>
<td>122 (5.5)</td>
<td>4220 (2.9)</td>
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</tr>
<tr>
<td>Surgical procedure</td>
<td></td>
<td></td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Parathyroidectomy</td>
<td>296 (13.4)</td>
<td>26,239 (18.0)</td>
<td></td>
</tr>
<tr>
<td>Partial thyroidectomy</td>
<td>915 (41.4)</td>
<td>63,662 (43.9)</td>
<td></td>
</tr>
<tr>
<td>Subternal thyroidectomy</td>
<td>125 (5.7)</td>
<td>4851 (3.4)</td>
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</tr>
<tr>
<td>Total thyroidectomy without neck dissection</td>
<td>777 (35.2)</td>
<td>45,944 (31.7)</td>
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<tr>
<td>Total thyroidectomy with neck dissection</td>
<td>97 (4.4)</td>
<td>4418 (3.0)</td>
<td></td>
</tr>
</tbody>
</table>

* Derived from χ² test for categorical variables and Student t test for continuous variables.

b Results for Native Americans, other, and unknown racial groups are not presented in this Table.

c Results for no charge and other insurance types are not presented in this Table.

d Residential income: the quartiles are identified by values of 1-4, indicating the poorest to wealthiest populations, respectively.
the NIS contains no patient identifiers, it does not require approval from the institutional review board.

Risk Factors

Patients’ demographics and clinical and hospital characteristics were examined as possible risk factors. Demographics included age at discharge, sex, race, insurance type, residential income, year of discharge, and geographic region. Hospital characteristics included hospital bed size, location of hospital (urban vs rural), teaching status of hospital, and hospital volume. Clinical characteristics included comorbidity score, obesity, smoking status, alcohol abuse, underlying diagnosis, and type of surgical procedure.

Using unique hospital identification numbers, we estimated hospital volume using a method previously described. First, we calculated the total number of thyroid and parathyroid operations for each hospital during the 10 study years. We then ranked hospitals in order of increasing total volume and selected a volume cutoff (75th percentile) that sorted hospitals into 2 groups: low and high volume. Comorbidities were identified using ICD-9-CM codes and used to calculate the modified Charlson Comorbidity Index (CCI). We divided patients on the basis of CCI score into 4 groups: 0, 1, 2, and ≥ 3. The most recent ICD-9 coding algorithm by Deyo et al was used to identify those comorbidities (see Sidebar: List of ICD-9-CM codes for comorbidities).

The underlying diagnoses were regrouped into four main groups as follows: parathyroid disease, benign thyroid diseases, thyroid cancer, and Graves disease. Types of surgical procedures were also regrouped into five main groups as follows: parathyroidectomy, partial thyroidectomy, substernal thyroidectomy, total thyroidectomy without neck dissection, and total thyroidectomy with neck dissection (see Sidebar: ICD-9-CM Diagnosis Codes and ICD-9-CM Procedure Codes).

Outcomes

The primary dependent variable of interest was the incidence of neck hematoma. Patient and hospital characteristics were examined as possible risk factors for neck hematoma after thyroid or parathyroid surgery. Secondary analyses were conducted to examine the clinical and economic consequences of neck hematoma by comparing the hospital charges, length of stay (LOS), and inhospital mortality between patients who experienced neck hematoma and those who did not. We then performed a series of multivariate logistic regression analyses using forward and backward stepwise methodology and simultaneous inclusion to calculate the odds ratio (OR) and p value for the association between patients’ and hospitals’ characteristics as independent risk factors for neck hematoma after thyroid or parathyroid surgery. Our objective was to define the models by keeping only the statistically significant and clinically relevant predictors using backward stepwise elimination of the nonsignificant predictors.

For all statistical analyses, considering the larger sample size in this study, the threshold for significance was 0.001. All analyses were generated using SAS software, Version 9.3 for Windows (SAS Institute Inc, Cary, NC).

RESULTS

We identified 147,344 thyroid and parathyroid operations that were performed between 2000 and 2009. Among those, 2210 patients (1.5%) experienced postoperative neck hematoma. The mean age at diagnosis was 57 years (vs 53 years for patients without neck hematoma). The median LOS was 3 days (vs 1 day for patients without neck hematoma). In univariate analyses, age at discharge, sex, race, type of insurance, residential income, year of discharge, geographic distribution,
smoking and alcohol abuse history, comorbidity, underlying diagnosis, and type of surgical procedure were found to have significant influence on the incidence of neck hematoma (p < 0.001). The risk of neck hematoma did not seem to be related to obesity. None of the hospital characteristics were statistically significant in the univariate analyses (Table 1).

Factors that were found to be statistically significant in the univariate analyses were included in the multivariate analyses. The results of multivariate analyses are presented in Table 2. Age 65 years and older (OR = 1.8, 95% confidence interval [CI] = 1.4-2.1), male sex (OR = 1.3, 95% CI = 1.2-1.4), African-American race (OR = 1.5, 95% CI = 1.2-1.7), being from the South (OR = 1.3, 95% CI = 1-1.4), comorbidity score of 3 or more (OR = 2, 95% CI = 1.6-2.6), history of alcohol abuse (OR = 2.7, 95% CI = 1.6-2.5), Graves disease (OR = 3, 95% CI = 2.1-4.1), and substernal thyroidectomy (OR = 3.3, 95% CI = 2.8-3.9) were associated with a higher risk of neck hematoma.

Table 3 presents the results of the multivariate analyses for the associations between neck hematoma and certain clinical and economic factors. Increased hospital charges were billed to approximately 60% of patients with neck hematoma, compared with only 23.7% of patients without neck hematoma (p < 0.001). The LOS was prolonged in 56.4% of those who had neck hematoma vs only 18% of those without neck hematoma (p < 0.001). The total number of deaths was 53 (2.4%) compared with 498 (0.3%) among patients without neck hematoma (p < 0.001; see Table 3).

### DISCUSSION

In this large nationwide study, we found that neck hematoma is rare after thyroid or parathyroid surgery but is associated with worse clinical and economic outcomes. Age, sex, race, geographic region, comorbidity, alcohol abuse, underlying diagnosis, and type of surgical procedure were found to be independent risk factors for neck hematoma. In contrast, none of the hospital-related factors (hospital bed size, location of hospital, teaching status of the hospital, and hospital volume) were found to be associated with increased risk of this complication.

The incidence of postoperative neck hematoma in our study (1.5%) was similar to that reported in the literature (0.1%-4.7%). Consistent with findings from previous studies, demographic characteristics such as older age

### Table 2. Multivariate adjusted analysis of risk factors for neck hematoma after thyroid and parathyroid surgery, Nationwide Inpatient Sample 2000-2009

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Number of events (%)</th>
<th>OR</th>
<th>CI</th>
<th>p value</th>
</tr>
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<tr>
<td>Age at discharge, years</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-40 (reference)</td>
<td>32,022</td>
<td>339 (1.1)</td>
<td>1.0</td>
<td>1.0</td>
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</tr>
<tr>
<td>41-65</td>
<td>78,540</td>
<td>1137 (1.4)</td>
<td>1.4</td>
<td>1.1-1.6</td>
<td>0.002</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>36,782</td>
<td>734 (2)</td>
<td>1.8</td>
<td>1.4-2.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Female (reference)</td>
<td>114,151</td>
<td>1498 (1.3)</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
<td>Male</td>
<td>32,033</td>
<td>708 (2.2)</td>
<td>1.3</td>
<td>1.2-1.4</td>
<td>&lt; 0.001</td>
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<td>Race</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>White (reference)</td>
<td>79,055</td>
<td>1054 (1.3)</td>
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<td>African American</td>
<td>15,973</td>
<td>351 (2.2)</td>
<td>1.5</td>
<td>1.2-1.7</td>
<td>&lt; 0.001</td>
</tr>
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<td>Hispanic</td>
<td>9803</td>
<td>115 (1.2)</td>
<td>0.9</td>
<td>0.7-1.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Asian</td>
<td>4451</td>
<td>66 (1.5)</td>
<td>1.3</td>
<td>1.0-1.7</td>
<td>0.04</td>
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<tr>
<td>Geographic region</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>West (reference)</td>
<td>34,442</td>
<td>432 (1.3)</td>
<td>1.0</td>
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<tr>
<td>South</td>
<td>48,110</td>
<td>860 (1.8)</td>
<td>1.3</td>
<td>1.1-1.4</td>
<td>&lt; 0.001</td>
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<tr>
<td>Northeast</td>
<td>35,992</td>
<td>426 (1.2)</td>
<td>0.9</td>
<td>0.8-1</td>
<td>0.37</td>
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<td>Midwest</td>
<td>28,800</td>
<td>492 (1.7)</td>
<td>1.2</td>
<td>1.1-1.4</td>
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<td>Charlson Comorbidity Index score</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0 (reference)</td>
<td>74,767</td>
<td>892 (1.2)</td>
<td>1.0</td>
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</tr>
<tr>
<td>1</td>
<td>19,574</td>
<td>342 (1.7)</td>
<td>1.4</td>
<td>1.2-1.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2</td>
<td>32,081</td>
<td>508 (1.6)</td>
<td>1.8</td>
<td>1.4-2.1</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>≥ 3</td>
<td>20,322</td>
<td>468 (2.3)</td>
<td>2.0</td>
<td>1.6-2.6</td>
<td>&lt; 0.001</td>
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<tr>
<td>Alcohol abuse</td>
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<td></td>
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</tr>
<tr>
<td>No (reference)</td>
<td>146,800</td>
<td>2183 (1.5)</td>
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<tr>
<td>Yes</td>
<td>544</td>
<td>27 (5)</td>
<td>2.7</td>
<td>1.6-2.5</td>
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<td>Diagnosis</td>
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<td></td>
</tr>
<tr>
<td>Parathyroid diseases (reference)</td>
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<td>386 (1.5)</td>
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<td>Benign thyroid disease</td>
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<td>1.2-1.8</td>
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<td>Thyroid cancer</td>
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<td>Graves disease</td>
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<td>122 (2.8)</td>
<td>3.0</td>
<td>2.1-4.1</td>
<td>&lt; 0.001</td>
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<td>Parathyroidectomy (reference)</td>
<td>26,555</td>
<td>296 (1.1)</td>
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<tr>
<td>Partial thyroidectomy</td>
<td>64,577</td>
<td>915 (1.4)</td>
<td>1.5</td>
<td>1.3-1.7</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Subtotal thyroidectomy</td>
<td>4976</td>
<td>125 (2.5)</td>
<td>3.3</td>
<td>2.8-3.9</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total thyroidectomy without neck dissection</td>
<td>46,721</td>
<td>777 (1.7)</td>
<td>1.7</td>
<td>1.5-2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total thyroidectomy with neck dissection</td>
<td>4515</td>
<td>97 (2.1)</td>
<td>2.3</td>
<td>1.7-4.7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

CI = confidence interval; OR = odds ratio.
and male sex were independent risk factors for neck hematoma. African-American race was an independent risk factor for neck hematoma in this study. Similarly, patients from the South had a higher risk of neck hematoma compared with patients from other regions. To the authors’ knowledge, no previous studies have examined race or geographic distribution as possible risk factors for this complication. Our findings are consistent with previous studies that failed to show any relation between obesity and risk of hematoma formation. The current study findings show an incremental trend in the incidence of neck hematoma from 2000 to 2009; this trend reaches statistical significance in the univariate but not the multivariate analyses. Promberger et al reported a progressive increase in the incidence of postoperative bleeding gradually over time, reaching 2.4% during 2004 to 2008. They also showed a decline in recurrent nerve injury during the study period, suggesting that the change in surgical technique that resulted in a decline in recurrent nerve injury did not lower the risk of postoperative bleeding.

The association between Graves disease and the risk of neck hematoma observed in our study has been previously reported in the literature. In a large retrospective series of more than 7000 patients undergoing thyroidectomy, the highest percentage of patients requiring a repeated intervention for hematoma were those with underlying Graves disease. Similarly, Palestini et al found a statistically significant higher prevalence of Graves disease in patients requiring repeated interventions for hematoma compared with case controls. Contrarily, Graves disease was significant on univariate analysis but not on multivariate analysis in two other studies, possibly because those studies were too underpowered to detect an independent association. Another limitation that affects accurately defining Graves disease as a risk factor for postoperative bleeding is the varying use of preoperative iodine (Lugol solution) among surgeons, for which we could not control. The increased vascularity of the thyroid in patients with Graves disease has been well documented. Furthermore, several well-conducted studies have proved the efficacy of Lugol iodine in decreasing thyroid parenchymal blood flow in these conditions.

We were surprised to find that benign but not malignant pathologic findings were associated with neck hematoma. Although neck hematoma was previously reported to increase in patients with malignant pathologic findings, recently, a large multi-institutional international study by Campbell et al reported a similar finding to our study. A possible explanation for this finding is that patients with benign pathologic findings frequently undergo thyroid lobectomy or subtotal thyroidectomy, which leaves behind vascularized thyroid tissue that could continue to bleed and lead to a hematoma. In fact, Chi et al, in a prospective randomized trial comparing bilateral subtotal thyroidectomy vs unilateral total thyroidectomy plus contralateral subtotal thyroidectomy for Graves disease, found a higher incidence of wound hematoma with the former. Most of the published series in the literature included only patients who underwent a thyroidectomy, with the

<table>
<thead>
<tr>
<th>Table 3. Comparison of patient clinical and economic outcomes by neck hematoma status, Nationwide Inpatient Sample 2000-2009, N = 147,344</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>Hospital charges above 75th percentile</td>
</tr>
<tr>
<td>Length of stay above 75th percentile</td>
</tr>
<tr>
<td>Death during hospitalization</td>
</tr>
</tbody>
</table>

* Derived from a $\chi^2$ test.
exception of two studies. Burkey et al\textsuperscript{12} included patients who underwent parathyroidectomy as well as thyroidectomy and identified an equal incidence of hematoma in the two groups. Rosenbaum et al\textsuperscript{13} reported no incidence of neck hematoma in the parathyroidectomy group. In our study, the incidence of neck hematoma after parathyroidectomy was lower than its incidence after thyroidectomy.

Although all types of thyroidectomies were found to be associated with a higher risk of hematoma compared with parathyroidectomy, subternal thyroidectomy seemed to carry the highest risk. Intrathoracic goiters have also been postulated to have a greater propensity for postoperative bleeding. This condition was found to be a statistically significant factor in one study.\textsuperscript{14} Goudet et al\textsuperscript{15} also noted a 2\% rate of early postoperative repeated operation for hemostasis in patients with subternal goiters compared with 1\% for a matched population with cervical goiters, but this was not found to be significant. Neck dissection was performed in a small percentage (4.3\%) of our patients, which is consistent with recent studies that report decreased use of neck dissection currently employed in minimal-access approaches to both the thyroid and parathyroid.\textsuperscript{1}

Previous research has shown that neck dissection performed during thyroid surgery is not associated with an increase in the risk of bleeding. In a large meta-analysis, Zhu et al\textsuperscript{22} reported results from 9 randomized controlled trials comparing total thyroidectomy with and without neck dissection among patients with thyroid cancer; results showed no difference in the risk of neck hematoma. In our study, both thyroidectomy with and without neck dissection was compared with parathyroidectomy as a reference group. The impact of thyroid resection on risk of bleeding was also evaluated in our study. Data regarding the impact of the extent of thyroid resection (partial vs total thyroidectomy) on the risk of neck hematoma are inconsistent. Several studies showed increased risk of bleeding when total thyroidectomy is performed compared with partial thyroidectomy.\textsuperscript{17,20} However, the extent of thyroidectomy did not have an impact on the rate of hematoma formation after thyroid surgery according to other studies.\textsuperscript{5,23} Again, we did not compare partial with total thyroidectomy. Instead, both partial and total thyroidectomy (with and without neck dissection) was compared with parathyroidectomy as a reference group. Although there was a statistically significant, progressive trend for the association between the extent of resection and risk of bleeding in our study (OR = 1.4, 1.7, and 2.1 for partial thyroidectomy, total thyroidectomy without and with neck dissection, respectively), the differences were small.

Another important finding of this study was the lack of association between hospital characteristics (including hospital volume) and our outcome of interest. A similar finding has been previously reported by Sosa et al.\textsuperscript{24} Sosa and colleagues speculated that most patients with thyroid disease are relatively young and otherwise healthy. As a result, a superior patient outcome generally does not require a large perioperative team of surgeons, intensivists, and consultants, or complex hospital equipment and monitoring. However, their speculation might not be applicable to our study as evident from the age (mean age = 57 years) and the comorbidity (44\% moderate or severe comorbidity) of our patients. Furthermore, hospital-related factors failed to reach statistical significance after adjusting for age, comorbidity, and other sociodemographic factors. Although surgeon volume was not evaluated in this study, findings from our previous unpublished work\textsuperscript{25} and several other studies\textsuperscript{26,27} have demonstrated the relation between surgeon experience and the risk of postoperative bleeding complications. Patients whose operations were performed by less experienced surgeons were more likely to experience complications postoperatively, including neck hematoma.

The current study was conducted using an administrative database and is subject to certain limitations. First, we did not have access to patient identifiers, and, thus, we could not link patient multiple admissions. Therefore, the study did not include patients who experienced this complication after discharge, which may have underestimated the incidence of neck hematoma. Also, for the same reason, we could not adjust for history of recurrent disease or previous surgery, which may increase the risk of neck hematoma.\textsuperscript{25,26} On the other hand, it must be noted that the NIS includes mostly inpatient admissions. Procedures performed in an outpatient setting may not be captured. Therefore, those patients might be high-risk patients, and our findings might not be applicable to all patients. Moreover, ICD-9-CM codes used to identify postoperative neck hematoma (998.11 and 998.12) are not specific to thyroid or parathyroid surgery. This may have resulted in capturing hemorrhages that occurred elsewhere in the body but were not necessarily caused by thyroid or parathyroid surgery, thus overestimating the incidence. Finally, the NIS lacks information on the details of the surgical technique such as suture ligation and use of certain hemostatic devices,\textsuperscript{27} postoperative vomiting, hypertension,\textsuperscript{28} use of drains, and use of antiplatelet and anticoagulation therapies, which have been postulated to affect the incidence of neck hematoma.\textsuperscript{18} Moreover, factors that were not accounted for, such as disorders of hemostasis, might be of importance. Finally, the NIS has no data on the weight of the thyroid gland, which is considered by many authors as the main predictor for neck hematoma.\textsuperscript{18}

\textbf{CONCLUSION}

Using a large nationwide database, we found that postoperative neck hematoma is a rare but potentially life-threatening complication and is associated with increased economic burden and resource utilization. Patients\' demographic and clinical characteristics, but not hospital factors, were associated with the risk of neck hematoma after thyroid or parathyroid surgery. However, all these factors except extent of surgery are patient related and, therefore, difficult to adjust. The extent of surgery might be reduced in some patients, but the choice of procedure is, in most cases, dictated by the disease. Accordingly, it seems
difficult to improve results by changing the identified risk factors. Nonetheless, surgeons should consider these factors when individualizing patient disposition after thyroid and parathyroid surgery.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Acknowledgments
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Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

References

The Best Physician
He is the best physician who is the most ingenious inspirer of hope.

— Samuel Taylor Coleridge, 1772-1834, English poet, literary critic, and philosopher

The Permanente Journal/ Winter 2015/ Volume 19 No. 1
Dr Haigh reports: “I was playing outside with my two kids. My eight-year-old daughter spotted a red-tailed hawk in a tree next door. My six-year-old son ran and brought his telescope. My daughter looked at the hawk through the telescope and told us that something was wrong with its eye. I looked and saw its left eye was white, and I thought it was an old injury or congenital defect! My daughter looked again and said, ‘Daddy, the hawk’s eye is perfectly normal.’ So I looked, but the eye was still white. We all swapped viewing through the telescope for several turns, and finally I noticed the left eye to be absolutely normal.

“We had discovered the nictitating membrane of a hawk—a translucent third eyelid found in some birds, reptiles, sharks, and seals that protects and moistens the eye—as seen covering its left eye on the bottom image. The uncovered right eye is on the top image. These two photographs were taken by holding my iPhone lens just above the eyepiece of the telescope.”

Dr Haigh is an Associate Editor of The Permanente Journal and an Oncologic and Endocrine Surgeon at the Los Angeles Medical Center in CA.
Upstream Discussion Provided in the Ambulatory Setting to Assist Patients with Chronic Kidney Disease Considering Dialysis

Tuan K Le, MD; Mi Chang, MD; Craig Nelson, PhD, CLS; Julie Ann Sortais, LCSW; Pushkar Chand, MD; Karen Tallman, PhD

ABSTRACT

Objectives: Extensive discussion with renal patients about treatment intensity is not systematically integrated into their care and often occurs during an acute hospitalization. We conducted a “test-of-change” pilot study to assess the utility of providing an upstream discussion in the ambulatory setting as an additional nephrology consult to assist patients with chronic kidney disease considering treatment choices.

Methods: We randomly assigned patients with Stage 4 or Stage 5 chronic kidney disease who had not yet begun renal dialysis to 1 of 2 groups. The test group received the additional nephrology consult and met with an interdisciplinary team composed of a nephrologist, social worker, and clinical ethicist, and the control group did not. Qualitative data were collected in 2012 and 2013 via oral questionnaire. Both groups received a 6-month follow-up assessment.

Results: Patients who received the nephrology consult reported that they experienced help in forming a treatment plan, felt well understood, and had the opportunity to thoroughly discuss questions. The controls had a 26% increased probability of beginning dialysis and had a statistically significant increase in dialysis and clinic visits (p < 0.10 and p < 0.05). Controls also were likelier than the test group to be admitted to the hospital (0.5 vs 0.2 admissions per patient in the test group), spend more days hospitalized (2.8 vs 0.5 bed days per patient), and visit the emergency room (0.73 vs 0.66 visits per patient) and clinic (6.6 vs 3.6 visits per patient).

Conclusions: An additional nephrology consultation proved helpful both qualitatively and quantitatively.

INTRODUCTION

It is important that patients participate in medical decision making. Specifically for patients with chronic kidney disease (CKD), there is a need for more thorough upstream treatment intensity discussions. One study by Davison indicated that of 584 patients with Stage 4 and Stage 5 CKD, 61% regretted their decision to start renal dialysis. Davison’s study identified gaps between current treatment practices and patient preferences for those with CKD. We were impressed by her data and the possibility that a more in-depth communication of prognosis and a more detailed discussion reviewing preferences for treatment planning could improve the routine care of patients with CKD.

The primary goal of our additional nephrology consult “test of change” was to assist patients with CKD, in the ambulatory setting, to make informed treatment planning decisions when their renal function markedly deteriorates. A test of change is a process that examines a small modification in patient care that can lead to a larger refinement when expanded to include a larger patient population. This additional nephrology consult test of change offered an important opportunity to measure whether the early decision-making conversations improved the overall care experience for patients with CKD. These discussions also attempted to help patients more thoroughly understand what it is like to receive dialysis and also to better comprehend the benefits of optimal conservative management without dialysis.

The aim of this test of change was to examine the utility of having an upstream discussion in the ambulatory setting that included introducing the Advance Directive for Health Care and Physician Orders for Life-Sustaining Treatment form. Operational issues affecting the delivery process of the consultation were examined, and statistical metrics were employed to evaluate the effectiveness of the additional nephrology consultation.

METHODS

Analysis of this test of change was approved by the Kaiser Permanente (KP) Southern California institutional review board. All consultations were held in the ambulatory setting and included patients and family members in 2012 and 2013 at KP South Bay Medical Center in Harbor City, CA. All sessions lasted approximately 2 hours. Each test patient had a consultation as part of our test protocol. This test of change used a random-assignment 2-sample test. The selection criteria for patients included age 80 years and older; CKD Stage 4 or Stage 5; one of the following comorbidities: malnutrition, dementia, or vascular disease (peripheral vascular disease, coronary artery disease, cerebrovascular disease); or patients referred from their primary nephrologist with a negative response to the surprise question...
“Would you be surprised if this patient dies within the next 6 to 12 months?”

Patients who fit the selection criteria were randomly assigned into 2 groups. The total participants numbered 30: 15 in the test group and 15 in the control group. Another 5 patients declined participation in the test of change. The test group received the additional nephrology consultation; the control group did not receive this consultation.

The additional nephrology consultation consisted first of a thorough case review and medical examination by the test-of-change nephrologist experienced and comfortable with discussing patients’ lived values and comfortable with exploring different treatment trajectories. This was followed by a patient and his/her family meeting with the entire consultation team, which was composed of the test-of-change nephrologist, a social worker, and a clinical ethicist. All consultation team members were the same individuals for the entire test of change. The family meeting included a clinical review of the patient’s short-term and long-term prognosis, questions patient or family members may have voiced, and a review of patient values and lived choices, as well as an introduction to the Advance Directive for Health Care and/or Physician Orders for Life-Sustaining Treatment form. Quantitative statistical analysis included χ² association between categorical variables, Bayes probability analysis, paired-differences t test, Z test, and Spearman rank order correlation (p). We used a significance level of 10% for our statistical analysis. Our hypothesis was that the data would exhibit a p value approaching 0.10 because of our small n. We were not confident a more

Structured Questions

- Did Dr ( ) and his/her team listen carefully to you and answer your questions fully?
- During this visit, did you feel you and your family were treated with dignity and respect?
- During the team’s visit, did you feel your wishes were understood and honored?
- Do you now feel you have a clear plan for your health care?
- After the visit, do you have a better understanding of your medical condition?
- Would you say this visit was very helpful, somewhat helpful, or not very helpful?
- Could you explain what made it that way?
- How could Dr ( ) and his/her team improve meetings with patients in the future?
- Is there anything else we should know?
- How would you rate the overall experience you’ve had with Dr ( )? (Outstanding, Excellent, Good, Adequate, or Poor)

Figure 1. Major iterative themes for the test group responding to the oral questionnaire.

Figure 2. Comparison of completed advance directives or Physician Orders for Life-Sustaining Treatment forms.*

*χ² = 1.2; p = 0.27. There was no statistically significant change at p < 0.10.
robust level of confidence (ie, 5%) would be achievable.

RESULTS

Figure 1 shows the results of the qualitative arm of the test of change for the additional nephrology consult. The major iterative themes for the test group responding to the oral questionnaire were that the consult was a helpful experience; the patients felt they had a clear plan after the consult, they favored the meeting format, they had their questions answered, and they felt understood. We also compared the completion of advance directives and/or Physician Orders for Life-Sustaining Treatment forms for the test group (those who received the additional nephrology consult) and for the control group (those who did not receive the test of change, the additional nephrology consultation).

Figure 2 shows that the test group had a higher percentage of completed advance directives and/or Physician Orders for Life-Sustaining Treatment forms than the control group. Although the increased amount of advance directives and/or Physician Orders for Life-Sustaining Treatment forms was encouraging, χ² analysis of our data showed no statistical significance at p < 0.10 (p = 0.27).

Statistical tests were used to analyze the data collected to determine if there was a statistically significant difference between the control group and the test group in dialysis use, hospital admissions, bed days, emergency room visits, and clinic visits. For dialysis use, Bayes probability showed that the control group had a 26% increase in dialysis use, and both the t test and the Z test also showed a statistically significant increase in dialysis use (p < 0.10 for both statistical tools). For hospital admissions, Spearman ρ showed a weak correlation (R = -0.342), and the Z test showed an increase in control group admissions (p < 0.05). When we analyzed bed day use and emergency room visits, the Spearman ρ showed a weak correlation (R = -0.154 and -0.154, respectively). The data collected for clinic visits when analyzed by t test showed an increase in clinic visits in the control group (p < 0.05), and the Spearman ρ showed a weak correlation (R = -0.402). Tables 1 and 2 detail all quantitative results.

DISCUSSION

Our test-of-change pilot study attempted to review the utility of providing an upstream discussion in the ambulatory setting for renal patients considering treatment plan decision making. It has been noted that treatment planning conversations must present "a clear understanding of the limits and possibilities of medicine and realize this understanding to be more of a process and not an epiphany."5 We believe this process is important for patients who need to clarify treatment goals6 in settings where more intense treatment options, such as commencing dialysis, may be a possible outcome of CKD. Interdisciplinary consultations in the ambulatory setting allow us to begin a conversation that can include helping patients and families better understand the possibilities of medicine, patients’ treatment goals, and lived values from the patients’ context.7 Documentation of this conversation in the patient's electronic medical record serves as a future reference.

CONCLUSION

The analysis described in this article showed that for a small cohort of patients, an additional nephrology consultation test of change proved helpful both qualitatively and quantitatively. It would be important to expand the test-of-change intervention to include a larger number of patients. When statisticians introduced ways of thinking about data, such as p values introduced by Ronald Fisher in the 1920s, tools of statistical analysis were seen as an informal way to judge whether evidence was worthy of a second look. We recommend that our work should be seen as Part 1 in a 2-stage analysis, and a second look should be seriously considered.8,9 Our exploratory test of change and data analysis gathered interesting and helpful findings. In the future, we encourage larger, more rigorous studies to be undertaken in this area.

Table 1. Quantitative analysis for control group

<table>
<thead>
<tr>
<th>Measure</th>
<th>t test</th>
<th>Spearman ρ</th>
<th>Z test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis</td>
<td>Increase in control group (p &lt; 0.10)</td>
<td>Unable to calculate correlation</td>
<td>Increase in control group (p &lt; 0.10)</td>
</tr>
<tr>
<td>Admissions</td>
<td>Increase in control group (p &gt; 0.10)</td>
<td>Weak correlation (R = -0.271)</td>
<td>Increase in control group (p &lt; 0.05)</td>
</tr>
<tr>
<td>Bed day use</td>
<td>Increase in control group (p &gt; 0.10)</td>
<td>Weak correlation (R = -0.342)</td>
<td>Increase in control group (p &gt; 0.10)</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>Increase in control group (p &gt; 0.10)</td>
<td>Weak correlation (R = -0.154)</td>
<td>Increase in control group (p &gt; 0.10)</td>
</tr>
<tr>
<td>Clinic visits</td>
<td>Increase in control group (p &lt; 0.05)</td>
<td>Weak correlation (R = -0.402)</td>
<td>Increase in control group (p &gt; 0.10)</td>
</tr>
</tbody>
</table>

* For Spearman rank order correlation (ρ), the sign of the coefficient indicates the direction of the relationship; if one variable tends to increase as the other decreases, the coefficient is negative. Statistical significance is p < 0.10.

1 Patients in the control group had a 26% increased probability of beginning dialysis, when data were analyzed by Bayes probability.

Table 2. Data on outcomes in control and test groups

<table>
<thead>
<tr>
<th>Measure</th>
<th>Control</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dialysis (no. of patients)</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Admissions</td>
<td>0.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Bed day use</td>
<td>2.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Emergency room visits</td>
<td>0.73</td>
<td>0.66</td>
</tr>
<tr>
<td>Clinic visits</td>
<td>6.6</td>
<td>3.6</td>
</tr>
</tbody>
</table>

* Data are expressed as number per patient except for dialysis.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.
Acknowledgment
Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

References

A True Impression
A straight answer does not mean for me what is often called the “blunt truth,” the “naked truth,” the dry cold facts. The truth that I mean is a true impression, a fully drawn and properly shaded account such as is, as I well know, very difficult to give … But better than either a misleading half truth or a pleasing lie, is an attempt to answer the patient’s question that he shall see not only what he can’t do and can’t hope for, but what he can do and what there is to work for hopefully.

— Richard C Cabot, MD, 1868-1939, American physician
Nasal Methicillin-Resistant Staphylococcus aureus Polymerase Chain Reaction: A Potential Use in Guiding Antibiotic Therapy for Pneumonia

Jennifer A Johnson, MD; Michael E Wright, PharmD; Lyndsay A Sheperd, PharmD; Daniel M Musher, MD; Bich N Dang, MD

INTRODUCTION

According to published guidelines, hospitalized patients at risk of methicillin-resistant Staphylococcus aureus (MRSA) pneumonia should receive empiric therapy for MRSA pending culture results. The principal limitations of this approach are that 40% to 70% of patients fail to produce adequate respiratory tract samples, and the processing of sputum specimens takes 72 to 96 hours. Therefore, patients empirically initiated on an anti-MRSA antibiotic regimen will certainly receive it for several days and probably remain on it for a full course of therapy. Overuse of antibiotics is associated with increased costs, drug-drug interactions, toxicity, and the development of antibiotic resistance.

Early identification of patients at very low risk of MRSA infection may spare them empiric antibiotic therapy directed against MRSA.

Nasal screening for MRSA with highly sensitive polymerase chain reaction (PCR) has a turnaround time of about one hour. This test is largely used for epidemiologic purposes; its usefulness as a tool for clinical decision making remains unclear. Nasal PCR results may help guide initial empiric antibiotic therapy for respiratory tract infections because the nasopharynx is generally regarded as the source of pathogens in bacterial pneumonia.

This study addresses a remarkably simple and focused question, namely, whether the absence of nasal colonization with MRSA (using nasal MRSA PCR) can predict the absence of MRSA in lower respiratory tract infections. We hypothesized that a negative nasal MRSA PCR correlates with the absence of MRSA in lower respiratory tract cultures, when both are collected within 48 hours of admission. If true, these results might guide empiric antimicrobial treatment of lower respiratory tract infection.

METHODS

We conducted a retrospective study of adult patients admitted to an urban teaching hospital (Baylor University Medical Center in Dallas, TX, with 1065 beds including 125 intensive care unit [ICU] beds) from September 2010 through October 2012. Inclusion criteria were 1) age 18 years or older; 2) MRSA nasal swab for PCR obtained within 48 hours of admission; and 3) a lower respiratory tract sample (sputum, tracheal aspirate, bronchoalveolar lavage, or bronchial wash or brush) obtained within 48 hours of hospital admission that yielded S aureus. We excluded patients transferred from another acute care facility. During the time of this study, ICU protocol required nurses to obtain a nasal MRSA PCR screen within 24 hours of ICU admission. Non-ICU patients underwent nasal PCR screening for MRSA at physician request. Lower respiratory tract cultures were obtained at the discretion of the physician; hospital protocol did not mandate surveillance cultures. Baylor Research Institute’s institutional review...
Table 1. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (N = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean)</td>
<td>55</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
</tr>
<tr>
<td>Female</td>
<td>30</td>
</tr>
<tr>
<td>Race and ethnicity</td>
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</tr>
<tr>
<td>Non-Hispanic white</td>
<td>32</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>29</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8</td>
</tr>
<tr>
<td>Asian</td>
<td>3</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>29</td>
</tr>
<tr>
<td>Neurologic disease</td>
<td>24</td>
</tr>
<tr>
<td>Obstructive pulmonary disease</td>
<td>18</td>
</tr>
<tr>
<td>Cancer</td>
<td>11</td>
</tr>
<tr>
<td>Tracheostomy</td>
<td>8</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
<td>5</td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>5</td>
</tr>
</tbody>
</table>

RESULTS

Seventy-two patients met inclusion criteria. Demographic and clinical characteristics are shown in Table 1. Lower respiratory tract samples included sputum (60%), tracheal aspirate (32%), and bronchoalveolar (8%) specimens. Forty-nine (68.1%) patients were admitted to the ICU, and 23 (31.9%) were admitted to the medical ward. Twenty-two (30.6%) patients died during the hospitalization.

Conditional probabilities are shown in Table 2. Of the 72 patients, 30 (42%) had cultures yielding MRSA and 42 (58%) had cultures yielding methicillin-sensitive *S. aureus*. Of the 30 patients with MRSA by culture, 28 had a positive nasal PCR, yielding a sensitivity of 93.3%. Of the 42 patients with positive cultures for methicillin-sensitive *S. aureus*, 40 had a negative MRSA nasal PCR, yielding a specificity of 95.2%. Twenty-eight of 30 patients with a positive nasal PCR had positive lower respiratory tract cultures for MRSA, giving a positive predictive value of 93.3%. Forty of 42 patients with a negative nasal PCR did not have positive lower respiratory tract cultures for MRSA, giving a negative predictive value of 95.2%.

DISCUSSION

A diagnostic test that correctly guides the discontinuation of empiric MRSA-directed antibiotic therapy must have a low false-negative rate, because a false-negative nasal MRSA PCR test could result in discontinuing MRSA-directed antibiotic therapy in a patient who actually has MRSA lower respiratory tract infection. In other words, we are interested in a test with high sensitivity and negative predictive value. The results of this study show that MRSA nasal PCR screening within 48 hours of admission has high sensitivity, specificity, and positive and negative predictive value for the presence of MRSA in lower respiratory tract culture. Given the low incidence of *S. aureus* community-acquired pneumonia (0.8%-3% in well-designed prospective studies), the nasal MRSA PCR test, with its high sensitivity and negative predictive value, could be a useful decision-making tool for clinicians to discontinue antibiotic coverage directed against MRSA early in admission. The principal benefits of the PCR screen include the ease of performing the nasal swab and rapid turnaround time. In addition, because respiratory tract samples are often difficult to obtain, the nasal MRSA PCR may be able to inform the discontinuation of MRSA-directed therapy in the absence of a respiratory tract sample.

Our study has several methodologic strengths. Unlike earlier investigators who obtained cultures from sputum and nonrespiratory sites (blood, incisions, and urine), we focused exclusively on the clinically relevant association between *S. aureus* colonization of the upper airways, in most cases the presumed source of bacteria that infect the lower respiratory tract, and the presence of MRSA in lower respiratory tract cultures. Secondly, we included only patients with lower respiratory tract cultures obtained within 48 hours of admission, thereby excluding patients with hospital-acquired infections. We also excluded patients transferred from another acute care facility for this reason.

Our study provides compelling data to undertake a more extensive prospective study. Moreover, the findings are consistent with a recent retrospective study in which the MRSA PCR test
had a sensitivity of 88% and a negative predictive value of 99.2% in predicting MRSA pneumonia. In contrast to this study, however, our study restricted patients to those with a nasal PCR collected within 48 hours. We selected a cutoff of 48 hours because studies indicate that nasal colonization status changes soon after hospital admission. The literature also suggests that nasal MRSA PCR has decreased sensitivity when clinical culture is obtained long after the PCR test. In a retrospective study of ICU patients by Byrnes et al, the sensitivity of nasal PCR screening for MRSA in clinical cultures was only 69.5%. The sensitivity was most diminished by the inclusion of cultures obtained after 7 days from the initial nasal swab PCR test. In fact, nasal swab PCR screening for MRSA was most sensitive when clinical cultures were obtained within 6 days of the PCR (79% vs 46%, p < 0.0001). Furthermore, Sarikonda et al determined that nasal screening with MRSA PCR was a poor predictor (sensitivity 24.2% and negative predictive value 84.4%) of ICU-acquired MRSA lower respiratory tract infections.

This study has certain limitations. We did not include all lower respiratory tract cultures, only those yielding *S. aureus*. However, our negative predictive value (ie, the probability that a negative nasal MRSA PCR correctly predicts a negative lower respiratory tract culture for MRSA) can only increase if all positive results of lower respiratory tract cultures were included. Our study was retrospective at a single institution. Given the study's retrospective nature, we do not know the correlation between culture results and lower respiratory tract disease. Because our hospital does not mandate surveillance cultures, presumably physicians ordered lower respiratory tract cultures when they suspected a lower respiratory tract infection. Nevertheless, our findings are still useful because a negative nasal PCR early during admission means that cultures of the lower respiratory tract are exceedingly unlikely (< 5%) to yield MRSA. Even earlier collection of MRSA nasal PCR and respiratory tract culture may improve correlation between tests. In a prospective study, samples could be collected within hours of hospital arrival, and even in the absence of an adequate respiratory tract specimen, PCR might provide data quickly enough to inform antibiotic decision making at admission. Last, because of the small scale of this study, our data are hypothesis generating rather than definitive. Nonetheless, we believe that this study has important implications for antibiotic stewardship. It also provides preliminary data for the conduct of a definitive multicenter prospective clinical study.

**CONCLUSION**

Nasal PCR for MRSA collected within 48 hours of admission appears to reliably predict the absence of MRSA in lower respiratory tract secretions. This test may have a role in guiding the discontinuation of MRSA-directed empiric antibiotic therapy for patients hospitalized with lower respiratory tract infections. Even though the number of patients in our study is small, the high sensitivity and negative predictive value for MRSA nasal PCR in *S. aureus* respiratory tract cultures is certainly suggestive that PCR for MRSA, when collected early in admission, reliably predicts the absence of MRSA in the lower respiratory tract. This warrants further exploration and a prospective study is needed to confirm these findings.

**Disclosure Statement**

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The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

**Acknowledgments**

At the time of this study, Jennifer A Johnson, MD, was a Pulmonary and Critical Care Physician in the Department of Internal Medicine at Baylor University Medical Center; Michael E Wright, PharmD, and Lyndsay A Shepard, PharmD, were Critical Care Clinical Pharmacists in the Department of Pharmacy at Baylor University Medical Center in Dallas, TX; Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

**References**

This image of a snowdrop blossom of the Galanthus genus was captured at Crystal Springs Rhododendron Garden in Portland, OR.

Dr. Shenson is an Internist at the Mt. Scott Medical Office in Clackamas, OR. More of his photography may be viewed at: www.davidshenson.com.
ABSTRACT

Objective: To investigate whether passive cigarette smoke exposure increases the risk of invasive pneumococcal disease in children.

Methods: In a population-based case-control study, 171 children aged 0 to 12 years with culture-confirmed invasive pneumococcal disease during the years 1994 to 2004 were identified. Two controls were matched to each case on age and patterns of Health Plan membership. We reviewed medical records of subjects and family members for information on household cigarette smoke exposure within 2 years of the diagnosis of invasive pneumococcal disease. We collected information on sex, race, pneumococcal vaccination, selected medical conditions, and medications in the 3 months before the diagnosis.

Results: Similar proportions of cases (25%) and controls (30%) had definite or probable passive smoke exposure (odds ratio [OR] = 0.76, 95% confidence interval [CI] = 0.47-1.2). Cases of invasive pneumococcal disease were more likely to be nonwhite than controls (OR = 4.4, 95% CI = 2.3-8.2). Elevated risk of invasive pneumococcal disease was found in subjects with recent pulmonary diagnoses (OR = 2.2, 95% CI = 1.2-4.0) and recent antibiotic use (OR = 1.6, 95% CI = 1.1-2.3).

Conclusions: Passive cigarette smoke exposure was not associated with invasive pneumococcal disease in this pediatric population. Invasive pneumococcal disease was associated with recent pulmonary diagnoses and recent antibiotic use.

INTRODUCTION

Streptococcus pneumoniae commonly causes bacterial infections among children. It is the predominant bacterial agent of acute otitis media, the most common pediatric outpatient diagnosis and reason for antibiotic prescriptions. It causes bacterial pneumonia among patients of all ages. Before routine immunization of US children with pneumococcal conjugate vaccine began in 2000, S pneumoniae was the most common bacteria in blood cultures from young febrile pediatric outpatients. Invasive pneumococcal disease, defined as isolation of S pneumoniae from a normally sterile site (eg, blood, cerebrospinal fluid, synovial fluid, pericardial fluid, pleural fluid, or peritoneal fluid), is more common among children younger than age 2 years. The potential relationship in children between environmental smoke exposure and pneumococcal disease has been reported. In The Gambia, invasive pneumococcal disease was associated with secondhand exposure to tobacco or cooking fire smoke. In Alaskan children, invasive pneumococcal disease was associated with a tobacco smoker living in the child’s household. In Finland, invasive pneumococcal disease among children was associated with smoking by the child’s mother. In a 2000 US case-control study of immunocompetent adults, invasive pneumococcal disease was associated with cigarette smoking and with passive smoking.

To investigate whether passive exposure to cigarette smoke increases the risk of invasive pneumococcal disease among children aged 0 to 12 years, we performed a population-based case-control study among members of a US integrated health care plan using Health Plan medical records.

METHODS

Subjects

This study was conducted in the population of the Kaiser Permanente Northwest (KPNW) Health Plan, which numbered 404,778 persons in 1994, including 9362 persons aged 0 to 2 years and 65,735 children aged 3 to 12 years. Cases of invasive pneumococcal disease were identified from a microbiology laboratory database or from medical records with the International Classification of Diseases, Ninth Revision (ICD-9) codes corresponding to invasive pneumococcal disease (038.x and 320.x). Cases identified through ICD-9 codes were not considered eligible unless the medical record documented that the S pneumoniae infection was confirmed by culture. Cases were collected from 1994 to 2004. These subjects were aged 0 to 12 years when the culture that yielded S pneumoniae was collected, and they had at least 1 month of Health Plan coverage before culture collection. The reference date was defined as the date of culture collection.

Two controls per case were randomly selected from KPNW membership files and were matched to cases by age. Health Plan membership on the reference date, and length of membership in KPNW before the reference date. We matched on Health Plan membership patterns to equalize access to past
medical history. Because our study design involved collecting information from the medical records of family members, we also matched cases and controls on whether the Health Plan account included the child alone (indicative of Medicaid and other publicly funded members) or the child plus others. KPNW’s institutional review board approved the study design and procedures. In our statistical power calculation assuming 170 cases with $\alpha = 0.05$ and a 2-tailed test, we estimated that we would have excellent power to detect an odds ratio (OR) of 2 or above and fair power to detect an association of 1.8.

Data Collection
Trained medical record abstractors reviewed the outpatient medical records of each case, each control, and all other individuals on their respective Health Plan account. Unless otherwise noted, we assumed that all persons listed on a Health Plan account were from one household. Persons eligible to enroll in a Health Plan account include the subscriber, a spouse or domestic partner, their children, their grandchildren, and other children for whom an eligible adult is the legal guardian.

We collected information about household exposure to passive cigarette smoke from birth through the reference date and, if documented, smoking history for all adults in the household. Information on household smoking is routinely collected from the medical records of all family members and manually coded the passive smoking variable for each subject. Three study investigators (CC, KR, SW) reviewed all smoking information collected from the medical records of all family members and classified as viral, bacterial, and fungal.

We categorized subjects as being at high-risk of invasive pneumococcal disease if they had any of the following diagnoses from birth to the reference date: chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, immunodeficiency, sickle cell anemia, cancer, chronic kidney disease, functional or anatomic asplenia, cerebrospinal fluid leak, and cystic fibrosis. Medical diagnoses in the three months before diagnosis of invasive pneumococcal disease were classified as ophthalmologic, ear/nose/throat (ENT), pulmonary, gastrointestinal, genitourinary, musculoskeletal, skin, neurologic, systemic, and infectious disease. Infectious disease was subclassified as viral, bacterial, and fungal.

For the main analysis, we compared subjects classified as either “definitely exposed” or “probably exposed” to passive cigarette smoke with those classified as either “definitely not exposed” or “probably not exposed.” A secondary analysis

<table>
<thead>
<tr>
<th>Exposure category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definitely exposed</td>
<td>All 3 of the following:</td>
</tr>
<tr>
<td></td>
<td>At least 1 person smokes recorded within 2 years of RD</td>
</tr>
<tr>
<td></td>
<td>No conflicting information from family members’ charts</td>
</tr>
<tr>
<td></td>
<td>No mention in child’s chart that smoker smokes outside</td>
</tr>
<tr>
<td>Probably exposed</td>
<td>Conflicting information on smoking in household but at least 1 record stating there is a smoker in household or</td>
</tr>
<tr>
<td></td>
<td>Meets criteria for “definitely exposed” and child’s record mentions that all smokers smoke outside or</td>
</tr>
<tr>
<td></td>
<td>Meets criteria for “definitely exposed” and only available information is recorded &gt; 2 years before RD</td>
</tr>
<tr>
<td>Probably not exposed</td>
<td>One parent is nonsmoker. No smoking information on other parent or</td>
</tr>
<tr>
<td></td>
<td>Child’s record states household is nonsmoking and 1 or more adults quit smoking within the last 5 years or quit at an</td>
</tr>
<tr>
<td></td>
<td>unknown date or</td>
</tr>
<tr>
<td></td>
<td>Any family member’s record states that no one in household smokes or</td>
</tr>
<tr>
<td></td>
<td>Both parents documented as nonsmokers or former smokers but information on at least one parent is &gt; 2 years before RD</td>
</tr>
<tr>
<td>Definitely not exposed</td>
<td>Unequivocal information from child’s record within 2 years before RD that no one in household smokes or</td>
</tr>
<tr>
<td></td>
<td>Information within 2 years before RD that both parents are nonsmokers. Any former-smoker parents quit more than 5 years before RD</td>
</tr>
<tr>
<td>Unknown</td>
<td>No smoking-related information found in subject’s or any family member’s medical record</td>
</tr>
</tbody>
</table>

RD = reference date (date of culture collection).
compared subjects classified as “definitely exposed” with those classified as “definitely not exposed”; although statistical power for this comparison was smaller, fewer misclassification errors were expected.

We evaluated the relationship between passive smoke exposure and invasive pneumococcal disease using conditional and unconditional logistic regression analysis; although controls were individually matched to cases, the general nature of the demographic matching variables permitted unconditional analysis. Results were very similar, and we report conditional results here for all analyses except the subanalysis comparing “definitely exposed” to “definitely not exposed,” for which we used unconditional logistic regression to retain subjects whose matched cases or controls had been excluded. For that analysis, conditional logistic regression produced a similar but less precise result because of exclusion of discordant cases and controls in the estimation. Conditional logistic regression results were adjusted for months of membership in the Health Plan during the last unbroken period of membership (linear) and earlier membership in the Health Plan (yes/no). The unconditional logistic regression model was further adjusted for the matching variables age (linear), Health Plan area (Portland, OR/Vancouver, WA metropolitan area vs Kelso/Longview, WA, and Salem, OR, areas), and whether family members were in the Health Plan (yes/no).

Because we did not know passive smoke exposure status for a substantial number of study subjects, we performed sensitivity analysis by bracketing exposure and comparing results. First, we put all subjects with unknown smoking history in the “definitely or probably exposed” group and ran the main logistic model; then we put all subjects with missing data in the “definitely not or probably not” exposed group and ran the main model again. We compared these results with a model in which we excluded subjects with unknown smoke exposure history. Results were similar, and we present the models excluding unknowns.

We evaluated for confounding by adding other potential risk factors one at a time to the smoke/invasive pneumococcal disease logistic models. We defined confounding as a change of more than 10% in the OR for smoke exposure/invasive pneumococcal disease with the potential confounder added to the model. Using multiplicative interaction terms and comparison of stratum-specific ORs, we assessed whether the smoke/invasive pneumococcal disease results differed according to the following characteristics: sex, race (white vs nonwhite), age group (0-2 years vs 3-12 years), high-risk status (yes/no), family members in Health Plan (yes/no), and years of conjugate vaccine availability (2000-2004 vs 1994-1999).

**RESULTS**

We identified 171 culture-confirmed invasive pneumococcal disease cases, all of whom presented with fever (Table 2). One hundred sixty-eight cases were identified from the laboratory database, and 3 were identified from ICD-9 codes. More than three-fourths of the cases (78%) were aged 2 years or younger. Cases were more likely than controls to be nonwhite (26% vs 10% of subjects with known race). During 1994-1999, the incidence of invasive pneumococcal disease was 26.8 cases per 100,000 person-years; 0.8% of cases and 0.4% of controls had received the pneumococcal polysaccharide vaccine, and the median number of invasive pneumococcal disease cases per year was 20. During 2000 to 2004, the incidence of invasive pneumococcal disease was 14.3 cases per 100,000 person-years; 19% of cases and 24% of controls had received pneumococcal conjugate vaccine, and the median number of annual cases decreased to 6.

Similar proportions of cases (25%) and controls (30%) had definite or probable passive smoke exposure (OR = 0.76, 95% confidence interval [CI] = 0.47-1.23; Table 3). For 20% of cases and 14% of controls, we were unable to find smoke exposure information. When we compared the “definitely exposed” group with the “definitely not exposed” group, results were similar (OR = 0.97, 95% CI = 0.50-1.88; Table 3); sensitivity analysis showed no material change in results (data not shown). These results were not confounded by sex, race, high-risk status, or other health conditions. Because of incomplete information in the medical record, we had insufficient information to assess confounding by history of being breastfed, daycare attendance, and number of household members.

<table>
<thead>
<tr>
<th>Table 2. Characteristics of cases and controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor</td>
</tr>
<tr>
<td>Cases (n = 171) No. (%)</td>
</tr>
<tr>
<td>Controls (n = 342) No. (%)</td>
</tr>
<tr>
<td>Source of case</td>
</tr>
<tr>
<td>Laboratory database</td>
</tr>
<tr>
<td>ICD-9 diagnoses</td>
</tr>
<tr>
<td>Year of diagnosis or reference date</td>
</tr>
<tr>
<td>1994-1999</td>
</tr>
<tr>
<td>2000-2004</td>
</tr>
<tr>
<td>Age group (years)</td>
</tr>
<tr>
<td>0-2</td>
</tr>
<tr>
<td>3-5</td>
</tr>
<tr>
<td>6-12</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>African American</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Not in medical chart</td>
</tr>
<tr>
<td>Family medical records available</td>
</tr>
<tr>
<td>Any pneumococcal vaccination (1994-2004)</td>
</tr>
<tr>
<td>1994-2004</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>Conjugate (2000-2004)</td>
</tr>
<tr>
<td>4 doses</td>
</tr>
<tr>
<td>2000-2004</td>
</tr>
<tr>
<td>4 doses</td>
</tr>
<tr>
<td>1-3 doses</td>
</tr>
</tbody>
</table>

ICD-9 = International Classification of Diseases, Ninth Revision; NA = not applicable.
We computed ORs for the association between invasive pneumococcal disease and other measured factors (Table 4). Cases of invasive pneumococcal disease were 4 times more likely to be nonwhite than controls. Children with the diagnosis of chronic asthma did not have a significantly elevated risk of invasive pneumococcal disease. However, a medical visit for asthma in the 3 months before the reference date was the most common pulmonary diagnosis. Of the 47 pulmonary diagnoses, the most common besides asthma were cough and bronchiolitis. During the 3 months before the reference date, subjects with pulmonary diagnoses had an elevated risk of invasive pneumococcal disease (OR = 2.2, 95% CI = 1.2-4.0).

The data also suggest an association between invasive pneumococcal disease and gastrointestinal diagnoses (OR = 1.8, 95% CI = 0.96-3.4), as well as with ENT conditions (OR = 1.33, 95% CI = 0.92-1.93). The association with ENT conditions was not substantially influenced by the specific diagnosis of otitis media (OR = 1.2, 95% CI = 0.78-1.84); the OR for the association of invasive pneumococcal disease with ENT conditions other than otitis media was 1.34 (95% CI = 0.80-2.23).

Antibiotic use during the 3 months before the reference date was related to invasive pneumococcal disease (Table 4). We observed higher ORs in children with 2 or more prescriptions during this period (OR = 2.1, 95% CI = 1.2-3.8) than in those with 1 prescription (OR = 1.4, 95% CI = 0.88-2.3). When we examined the timing of the most recent prescription, ORs for 0 to 30 days, 31 to 60 days, and 61 to 90 days before the reference date were 1.9 (95% CI = 1.1-3.2), 1.6 (95% CI = 0.89-3.0), and 1.2 (95% CI = 0.60-2.5), respectively.

Overall, few subjects had received pneumococcal vaccination (6% of cases, 8% of controls). During a nationwide shortage of pneumococcal conjugate vaccine from November 2003 to September 2004, many children 0 to 2 years of age received only the first 1 to 3 doses of the 4-dose series per recommendations from the Centers for Disease Control and Prevention in Atlanta, GA.

**DISCUSSION**

Parental cigarette smoking has been associated with increased nasopharyngeal carriage of pneumococci in children.10 Cigarette smoke exposure decreases mucociliary clearance,11 enhances bacterial adherence to the respiratory epithelium,12 and increases the permeability of the respiratory epithelium.13 Passive smoke exposure is also associated with an increased incidence of viral upper respiratory tract infections,14 which have been related to increased occurrence of invasive pneumococcal disease14; near doubling of the risk of developing a serious lower respiratory tract infection requiring hospitalization, especially in children younger than 2 years of age15; and a 28% increase in hospitalization for pneumonia and bronchitis in infants of mothers who smoke.16

Cigarette smoking is associated with alterations in immune system function, including decreased levels of circulating immunoglobulins, decreased natural killer cell activity, depressed neutrophil chemotaxis and phagocytic activity, and decreased release of proinflammatory cytokines.17 Further research is

### Table 3. Relation between cigarette smoke exposure and invasive pneumococcal disease

<table>
<thead>
<tr>
<th>Smoke exposure category</th>
<th>Cases (n = 342)</th>
<th>Controls (n = 342)</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely not exposed or probably not exposed</td>
<td>94 (55)</td>
<td>191 (56)</td>
<td>Reference</td>
</tr>
<tr>
<td>Definitely exposed or probably exposed</td>
<td>43 (25)</td>
<td>103 (30)</td>
<td>0.76 (0.47-1.23)</td>
</tr>
<tr>
<td>No information in chart</td>
<td>34 (20)</td>
<td>48 (14)</td>
<td>—</td>
</tr>
<tr>
<td>Subjects classified as “definite”</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definitely not exposed</td>
<td>35 (60)</td>
<td>85 (63)</td>
<td>Reference</td>
</tr>
<tr>
<td>Definitely exposed</td>
<td>23 (40)</td>
<td>50 (37)</td>
<td>0.97 (0.50-1.88)</td>
</tr>
</tbody>
</table>

* Conditional logistic regression odds ratio adjusted for receipt of any pneumococcal vaccine and patterns of Health Plan membership. This analysis used 132 case-control sets with smoke exposure data on the case (n = 132, 30% exposed) and at least 1 of the 2 matched controls (n = 239, 35% exposed).

### Table 4. Demographics and medical history in relation to invasive pneumococcal disease

<table>
<thead>
<tr>
<th>Factor</th>
<th>Cases (n = 171) No. (%)</th>
<th>Controls (n = 342) No. (%)</th>
<th>Odds ratio* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>83 (49)</td>
<td>184 (54)</td>
<td>0.84 (0.58-1.22)</td>
</tr>
<tr>
<td>Nonwhite raceb</td>
<td>34 (20)</td>
<td>19 (6)</td>
<td>4.37 (2.32-8.22)</td>
</tr>
<tr>
<td>Chronic conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-risk for IPDc</td>
<td>18 (11)</td>
<td>24 (7)</td>
<td>1.51 (0.77-2.94)</td>
</tr>
<tr>
<td>Chronic asthma</td>
<td>13 (8)</td>
<td>22 (6)</td>
<td>1.18 (0.57-2.45)</td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td>11 (6)</td>
<td>26 (8)</td>
<td>0.49 (0.12-2.03)</td>
</tr>
<tr>
<td>Diagnoses/events at visit &lt; 3 months before reference date</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>66 (39)</td>
<td>97 (28)</td>
<td>1.57 (1.08-2.33)</td>
</tr>
<tr>
<td>Ophthalmologic ICD-9</td>
<td>10 (6)</td>
<td>22 (6)</td>
<td>0.92 (0.42-1.99)</td>
</tr>
<tr>
<td>ENT ICD-9</td>
<td>76 (44)</td>
<td>128 (37)</td>
<td>1.33 (0.92-1.93)</td>
</tr>
<tr>
<td>Otitis media</td>
<td>46 (27)</td>
<td>81 (24)</td>
<td>1.20 (0.78-1.84)</td>
</tr>
<tr>
<td>Nonotitis media ENT ICD-9</td>
<td>30 (18)</td>
<td>47 (14)</td>
<td>1.34 (0.80-2.23)</td>
</tr>
<tr>
<td>Pulmonary ICD-9</td>
<td>24 (14)</td>
<td>23 (7)</td>
<td>2.20 (1.20-4.02)</td>
</tr>
<tr>
<td>Gastrointestinal ICD-9</td>
<td>19 (11)</td>
<td>21 (6)</td>
<td>1.81 (0.96-3.41)</td>
</tr>
<tr>
<td>Genitourinary ICD-9</td>
<td>6 (4)</td>
<td>7 (2)</td>
<td>1.77 (0.58-4.41)</td>
</tr>
<tr>
<td>Musculoskeletal ICD-9</td>
<td>5 (3)</td>
<td>6 (2)</td>
<td>1.59 (0.48-5.23)</td>
</tr>
<tr>
<td>Skin disease ICD-9</td>
<td>11 (6)</td>
<td>46 (13)</td>
<td>0.45 (0.22-0.90)</td>
</tr>
<tr>
<td>Neurologic ICD-9</td>
<td>4 (2)</td>
<td>10 (3)</td>
<td>0.79 (0.24-2.61)</td>
</tr>
<tr>
<td>Systemic disease ICD-9</td>
<td>8 (5)</td>
<td>10 (3)</td>
<td>1.69 (0.62-4.61)</td>
</tr>
<tr>
<td>Any infectious disease</td>
<td>85 (50)</td>
<td>146 (43)</td>
<td>1.33 (0.92-1.92)</td>
</tr>
<tr>
<td>Infectious disease: viral ICD-9</td>
<td>14 (8)</td>
<td>21 (6)</td>
<td>1.33 (0.65-2.72)</td>
</tr>
<tr>
<td>Infectious disease: fungal ICD-9</td>
<td>1 (1)</td>
<td>4 (1)</td>
<td>0.52 (0.06-4.70)</td>
</tr>
<tr>
<td>Infectious disease: bacterial ICD-9</td>
<td>5 (3)</td>
<td>5 (1)</td>
<td>1.80 (0.51-6.34)</td>
</tr>
</tbody>
</table>

* Conditional logistic regression odds ratios adjusted for patterns of Health Plan membership.

b Subjects with missing data on race (25% of cases and 51% of controls) were considered as white in this analysis.

c Includes asthma, chronic cardiac disease, chronic pulmonary disease, diabetes mellitus, immune deficiency, sickle cell anemia, cancer, chronic kidney disease, functional/anatomic asplenia, cerebrospinal fluid leak, and cystic fibrosis.

CI = confidence interval; ENT = ear/nose/throat; ICD-9 = International Classification of Diseases, Ninth Revision; IPD = invasive pneumococcal disease.
needed to investigate whether similar immune alterations occur among children with passive smoke exposure.

Epidemiologic research on cigarette smoke exposure and invasive pneumococcal disease in children is limited. Among Alaskan Native children aged 0 to 2 years, the risk of invasive pneumococcal disease was associated with presence of at least 1 tobacco smoker in the household and smokeless tobacco use by a household contact. The small study size (29 cases, 85 controls) limited statistical power to evaluate these associations, particularly in multivariate analysis. Among children in Finland, daycare attendance and frequent otitis media were significantly associated with invasive pneumococcal disease in 0- to 2-year-old children, and among children aged 2 to 15 years, having a preschool-aged sibling was a risk factor. Presence of a parent smoking daily inside the home did not increase the risk of invasive pneumococcal disease.

In a study of 0- to 15-year-old children in Spain, the risk of invasive pneumococcal disease was associated with siblings younger than age 15 years and with day nursery attendance. There was no significant association with smokers living in the child’s home or with the number of cigarettes smoked in the home. Our finding of no association between passive smoke exposure and invasive pneumococcal disease agrees with 2 of the aforementioned studies and a meta-analysis of the 1975-2009 literature.

A large case-control study demonstrated that asthma was a risk factor for invasive pneumococcal disease among 2- to 17-year-old children. Our study’s association of a pulmonary diagnosis during the 3 months before the reference date with invasive pneumococcal disease may reflect asthma as a risk factor because the most common pulmonary diagnosis was asthma. Among the many 0- to 2-year-old subjects, an age group in whom asthma can be difficult to diagnose, some subjects diagnosed with cough or bronchiolitis may have been asthmatic.

Our finding that a higher proportion of cases of invasive pneumococcal disease than controls are nonwhite was previously described. In the US, African Americans, Alaskan Natives, and certain American Indians have a twofold to threefold higher rate of invasive pneumococcal disease compared with whites. Possible reasons for more invasive pneumococcal disease among nonwhites include differences in medical care-seeking behavior and factors related to low socioeconomic status, such as transmission of respiratory diseases in crowded housing.

Other reported risk factors for invasive pneumococcal disease in children 2 to 59 months of age in North America include underlying illnesses (immunodeficiency HIV infection, sickle cell disease, cancer, kidney disease, asplenia, or splenic dysfunction); daycare attendance in the preceding 3 months; antibiotic use within the preceding 3 months; and lack of breastfeeding. Our finding of a positive association with recent antibiotic use agrees with the findings of Takala et al12 and Levine et al13 and is expected because an antibiotic prescription is a surrogate marker for likely bacterial infection. Few children in our study had high-risk medical conditions, so we had little power to explore that association.

Limitations of our analysis include possible exposure misclassification. Health Plan members could share a Health Plan account yet live in different households, or children could be exposed to smoke from caregivers outside the home. Another limitation is that medical records may contain underreporting of smoking activity. We lacked information to adjust for breastfeeding, daycare attendance, or number of household members.

The relationship between invasive pneumococcal disease and recent pulmonary diagnoses is probably because of S pneumoniae causing bacterial pneumonia, bronchiitis, sinusitis, and otitis media in children. Subjects with asthma may be more susceptible to invasive pneumococcal disease because of corticosteroid treatment of reactive airway disease or injured lower respiratory tract epithelium.

It is difficult to speculate on reasons for the possible association between recent gastrointestinal conditions and invasive pneumococcal disease. To our knowledge, our study is the first to report this association.

CONCLUSION

In this largest study to date examining whether passive smoke exposure increases the risk of invasive pneumococcal disease in children, we did not observe a positive association, as has been described in adults. Ascertainment of passive smoke exposure from medical records was incomplete for 16% of subjects; however, sensitivity analysis confirmed that results were unchanged when subjects with unknown smoke exposure were classified as exposed or as unexposed. Given the incidence of smoking and the morbidities associated with passive smoke exposure, improved documentation of smoke exposure in the child’s medical record is needed to facilitate better assessment of the patient’s disease risk, target smoke avoidance advice, and counsel household contacts regarding tobacco cessation. The association of invasive pneumococcal disease with recent pulmonary diagnoses and with recent antibiotic use should be investigated further.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Acknowledgment
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Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

References

Who Could Stay and Not Perish

Smoking is … markedly impolite, an impertinent unsociability. Smokers poison the air near and far and suffocate every honest person who cannot defend himself by smoking in his turn. Who on earth can enter the room of a smoker without getting nauseated? And who could stay and not perish?

—Johan Wolfgang von Goethe, 1749-1832, German writer and statesman
ABSTRACT

Context: Medical journals have allowed researchers to share their latest discoveries, especially in the most common diseases affecting patients worldwide.

Objective: To analyze trends in the frequency of original research into common dermatologic diseases from 1970 to 2010.

Design: A retrospective review of the Journal of the American Academy of Dermatology and the Archives of Dermatology was performed using the MEDLINE database. All original research articles published between 1970 and 2010, by quinquennium, dealing with acne vulgaris, rosacea, skin cancer, dermatitis, psoriasis, or skin infections were included.

Main Outcome Measure: Total number of publications dealing with each dermatologic topic considered.

Results: The frequency of research into acne vulgaris and rosacea decreased from 24% in 1970 to 5.1% in 2010. Psoriasis research increased in frequency from 17.6% to 26.5% from 2000 to 2010, and skin cancer research increased from 4% in 1970 to 48% in 2010.

Conclusions: Topics that experienced early advancements in research, such as acne vulgaris and rosacea, demonstrated a decreasing trend in the frequency of publication. Published psoriasis research has increased in frequency since 2000, most likely because of the discovery of biologics. Finally, skin cancer research has continued to increase in frequency of publication, paralleling the increasing incidence of skin cancer.

INTRODUCTION

As described by Sharma and Sawhney in their review article, the last century has seen monumental advancements in the field of dermatology. The extraction of retinol from egg yolk in 1909 gave rise to topical and oral retinoids for the treatment of acne. Topical corticosteroids were discovered in 1935, providing anti-inflammatory activity for numerous skin diseases such as contact and atopic dermatitis. Modern-day phototherapy began in 1923, leading to the US Food and Drug Administration’s approval of psoralen-ultraviolet A for psoriasis in 1982. Frederic Mohs, MD, introduced Mohs dermatosurgery in 1936, providing remarkable cure rates for basal cell and squamous cell carcinoma. Additionally, the development of antimicrobial agents over the years has provided successful treatment of numerous skin infections.

These and countless other advancements have been documented through publications in various medical journals devoted to dermatology. The first of these, the Journal of Cutaneous and Venereal Diseases (later known as the Archives of Dermatology and now as JAMA Dermatology), was first published in October 1882. Since then, dermatology journals have provided an opportunity for researchers to share their latest work in the field, a collaborative effort to ultimately bring forth the best medical care to patients. A recent study demonstrated trends in the type of original dermatology research published in these journals, but little is known about how the subject matter of research has changed over time.

The purpose of our study was to determine trends in the frequency of original research into common dermatologic diseases published in two foremost American dermatology journals, the Journal of the American Academy of Dermatology (JAAD) and Archives of Dermatology, by analyzing the years 1970 to 2010 by quinquennium.

METHODS

We conducted a search of the MEDLINE database, extracting print versions of all articles published in JAAD and Archives of Dermatology for the calendar years of 1970, 1975, 1980, 1985, 1990, 1995, 2000, 2005, and 2010. There were no articles from JAAD in 1970 and 1975 because the first publication of JAAD was in 1979. Only articles meeting one of the specified subject matter criteria and considered to be original research were included in the study. Original research articles were identified as having a clearly stated objective, well-defined methods, and a results section.

Table 1. Number of original dermatologic research articles by quinquennium, 1970-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of articles</th>
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<tbody>
<tr>
<td>1970</td>
<td>25</td>
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<tr>
<td>1975</td>
<td>29</td>
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<td>33</td>
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<td>2000</td>
<td>85</td>
</tr>
<tr>
<td>2005</td>
<td>123</td>
</tr>
<tr>
<td>2010</td>
<td>98</td>
</tr>
</tbody>
</table>

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The study type (e.g., clinical trial, basic science, retrospective, cross-sectional) was not a discriminating factor for inclusion in the study. Case reports, review articles, meta-analyses, editorials, and educational materials were excluded.

The subject matter criteria for this study were based on the most commonly encountered outpatient dermatologic diagnoses: acne vulgaris/rosacea, skin cancer, dermatitis, psoriasis, and skin infections. Acne vulgaris and rosacea were classified together because of their similarity as acneiform disorders. For skin cancer, only the three most common types were considered: basal cell carcinoma, squamous cell carcinoma, and melanoma. A classification of dermatitis was assigned for studies addressing atopic dermatitis, contact dermatitis, or seborrheic dermatitis. Psoriasis was also one of the included subject matters. Finally, a classification of skin infections was assigned for studies addressing viral, bacterial, fungal, or parasitic infections of the skin, hair, nails, or mucous membranes. Examples included herpes simplex, varicella, human papillomavirus, molluscum contagiosum, cellulitis, abscesses, Lyme disease, syphilis, dermatophytosis, tinea versicolor, scabies, and lice. If an article dealt with more than one possible subject matter, the topic that best fit the primary objective of the article was chosen.

RESULTS

Original Research Articles

The study included 620 published original research articles dealing with at least one of the aforementioned topics. There was a relatively linear increase in the number of original research articles from 1970 to 2010. In both JAD and Archives of Dermatology, the peak number of original research articles occurred in 2005, which produced 123 articles (Table 1). Moreover, both JAD and Archives of Dermatology saw the largest percentage increase in original articles between 1985 and 1990—109% and 74% increases, respectively.

Trends in Subject Matter

The subject matter that composed the largest proportion of the collected articles was skin cancer (36.5%), followed by psoriasis (23.7%), skin infections (18.2%), dermatitis (15%), and acne/rosacea (6.6%). In JAD, acne/rosacea was the most frequent topic at 38.5% in 1980, followed by a precipitous decline to 1.9% in 1995 and leveling to approximately 7.5% in 2010. Skin cancer consisted of 30.8% of articles in 1980, with a gradual increase in the past decade to 40.5% in 2005 and to 35.8% in 2010. Dermatitis showed a gradual decrease from 23.1% in 1980 to 19.2% in 1995 and 15.1% in 2010. Psoriasis peaked at 40.6% in 1985, with a sharp decline to 14.9% in 1990, but increased back to 23.4% in 2000 and 30.2% in 2010. Skin infections trended upward from 1980, peaking at 32.8% in 1990, followed by a relatively linear decline to 11.3% in 2010 (Figure 1). In Archives of Dermatology, acne/rosacea consisted of 24% of articles in 1970, declining to around 5% to 7% from 1975 to 2005, reaching 2.2% in 2010. Skin cancer represented the smallest proportion of articles in 1970 at 4% but witnessed a continued rise to 35% in 1980, 47.4% in 2000, and 62.2% in 2010. Dermatitis remained relatively stable throughout the years, starting at 12% in 1970, peaking at 18.4% in 2000, and returning to 11.1% in 2010. Psoriasis was the most prevalent of the topics considered in 1970 at 32% but...
began to decrease in 1985, reaching a low of 10.5% in 2000. Recent years, however, have shown an increase back to 18.4% in 2005 and 22.2% in 2010. Skin infections demonstrated a bimodal trend, decreasing from 28% in 1970 to 10% in 1980. This was followed by a peak of 30.3% in 1990 and a subsequent decline to 2.2% in 2010 (Figure 2). When articles from JAAD and Archives of Dermatology were combined and analyzed together, acne/rosacea declined from 24% in 1970 to 4% in 1990 and 5.1% in 2010. Skin cancer demonstrated an increasing trend from 4% in 1970 to 31% in 1990 and 48% in 2010. Dermatitis showed a small increase from 12% in 1970 but roughly remained at 15% to 17% throughout the past 3 decades. Psoriasis showed much variability from 1970 to 1990 but demonstrated a recent increase from 17.6% in 2000 to 19.5% in 2005 and 26.5% in 2010. Finally, skin infections demonstrated a continuous decline from a peak of 32% in 1990 to 20% in 2000 and 7.1% in 2010 (Figure 3).

DISCUSSION

A critical component of modern medicine has been the publication of research in medical journals, allowing investigators to share their latest discoveries with the world. In dermatology, some of the most commonly encountered diseases are acne vulgaris, rosacea, skin cancer, dermatitis, psoriasis, and skin infections. By studying trends in the prevalence of original research into these subject matters, we attempted to provide a historical perspective as well as a commentary on the future direction of research in the field.

We found that original research publications into the most common dermatologic topics have grown steadily since 1970, which is not surprising because dermatology has continued to grow as a medical specialty. Interestingly, both JAAD and Archives of Dermatology demonstrated a similar period of rapid growth in original research, around 1985 to 1990, as well as a peak in the number of publications around 2005. This may coincide with the fact that the “golden era” of discovering new classes of antibiotics ceased in the 1970s, followed by a resurgence of interest in the 1990s as a result of emerging antibiotic resistance.

Epidemiologic studies have shown that psoriasis is an increasingly common disease, which has almost doubled in annual incidence since the 1970s. We found that the prevalence of psoriasis research initially showed a variable course, with an eventual downward trend around 1990, but has seen a steady increase since 2000. This may be largely attributable to the development of tumor necrosis factor inhibitor therapy around this time, which has proved to be very successful in the treatment of psoriasis.

Nevertheless, recent studies on genetic variations between Propionibacterium acnes strains, a potential bacteriophage-based treatment for acne, and the continual search for a microbial cause of rosacea offer an exciting future for research in these topics. Research into dermatitis has stayed relatively stable since 1970, especially in recent years. Although contact dermatitis and seborrheic dermatitis were included in this category, atopic dermatitis has been the main topic of research. A possible explanation for this steady trend includes the relatively recent insights into the pathogenesis of the disease, fueled by joint interest and research from allergy and immunology. Moreover, a 2006 study by Asher et al showed that the worldwide prevalence of eczema was increasing, especially in developing nations. Regarding skin infections, we found that original research peaked around 1970 and 1990, followed by a steady decline since then. This correlates with the fact that the continual search for a microbial cause of rosacea offer an exciting future for research in these topics.

Another interesting finding in our study was that research into skin cancer has continuously increased over time, even in the past decade. We believe this has been driven in large part by advances in melanoma research. As mentioned in the report from the third Melanoma (Research) Bridge meeting,
in December 2012, a “new era” of targeted and immune-based therapies for melanoma has been ushered in by recent findings. Moreover, the National Cancer Institute has increased funding for melanoma research in recent years from $102.3 million in 2010 to $121.2 million in 2012. Continued research into skin cancer is critical, as studies have shown an increase in the incidence of melanoma and nonmelanoma skin cancers.

We acknowledge limitations in our study. Access to journal articles was limited by our university’s subscriptions. Further, multiple topics were categorized under one topic, considered the best fit by the reviewer. However, this occurred rather infrequently. We also analyzed trends in research based on one year of research for every five years. This may not have been representative of the timeframe because of sampling error. In addition, there were no publications in JAD in the years 1970 and 1975, so analysis during this period was limited to Archives of Dermatology.

CONCLUSIONS

We have demonstrated trends in the frequency of original research into common dermatologic topics, with an attempt to explain some of our findings in a historical context. We have discovered that dermatology research has paralleled clinical needs, a testament to the ability of modern medicine to continually answer the call for innovation. We believe our findings bring further optimism to a bright future for research in dermatology.

Disclosure Statement

Dr Wu received research funding from Abbott Laboratories, Abbott Park, IL; AbbVie, North Chicago, IL; Amgen Inc, Thousand Oaks, CA; Eli Lilly, Indianapolis, IN; Merck, Whitehouse Station, NJ; and Pfizer, New York, NY, which were not directly related to this study. Mr Cho has no conflicts of interest to disclose. No funding was received for this study.

Acknowledgment

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

References


A Winter Walk
photograph
Sally J Cullen, MD, MS

This photograph was taken from the boardwalk on the shore of Mono Lake in Mono Lake Tufa State Reserve in CA. The reserve was established to protect the lake surface; its surrounding wetlands, which are visited by millions of birds each year; and the iconic calcium-carbonate spires rising from the lake. The spires were formed by the interaction between freshwater springs and the highly alkaline lake water.

Dr Cullen retired in 2012 as Assistant Chief of Pediatrics at Kaiser Permanente Folsom in CA. For her, photography is a way of capturing and celebrating beauty, especially of the natural world. More of her work may be viewed at: www.myparkphotos.com/property/SallyCullen.html.
ORIGINAL RESEARCH & CONTRIBUTIONS

Intervention to Reduce Inappropriate Ionized Calcium Ordering Practices: A Quality-Improvement Project

Darrell B Newman, MD; Konstantinos C Siontis, MD; Krishnaswamy Chandrasekaran, MD; Allan S Jaffe, MD; Deanne T Kashiwagi, MD

ABSTRACT

Context: The importance of an abnormal ionized calcium (iCa) measurement in noncritically ill patients is unclear. Furthermore, iCa monitoring is more expensive than measurement of total calcium and consumes more laboratory resources. We hypothesize that most iCa tests are ordered for routine monitoring in asymptomatic patients, and results do not influence clinical management.

Objective: To characterize and to intervene on iCa testing ordering practices among our institution's hospital-based internal medicine clinicians.

Design: A quality-improvement project, with retrospective review of clinical records. We retrospectively identified the first 100 consecutive patients admitted to our hospital internal medicine (HIM) services during January 2012 with an iCa test ordered during their hospitalization. We reviewed clinical records to determine the appropriateness of iCa test ordering and of the ordering department. An educational intervention regarding the appropriateness of iCa testing was undertaken targeting HIM clinicians.

Main Outcome Measures: The effect of the intervention was assessed by identifying a sample of the first 100 consecutive patients admitted to HIM services during November 2012 and by comparing the proportion of iCa tests ordered by HIM clinicians before and after the intervention.

Results: HIM services were responsible for 38% of iCa measurements before the educational intervention, with the remainder originating primarily from the Emergency Department (29%) and intensive care units (28%). After the intervention, the internal medicine services were responsible for 13% of iCa measurements, which represented a 66% reduction (p = 0.0007).

Conclusion: A simple intervention based on clinician education can reduce the frequency of routine iCa monitoring in stable hospitalized patients.

INTRODUCTION

Calcium homeostasis is critical for maintaining the physiologic functioning of most major organ systems in health and in disease. Although population studies have defined normal ranges of serum total calcium and serum ionized calcium (iCa) in healthy subjects, little is known about “optimal” total calcium and iCa in acutely and/or critically ill patients. In fact, neither observational nor experimental studies are available to guide management in this setting. It is possible that parenteral supplementation might be detrimental in the long term. Indeed, this controversial topic was highlighted in a prior Cochrane systematic review examining the effects of calcium supplementation in intensive care unit (ICU) patients. Additional concerns related to iCa monitoring are the increased cost and laboratory resource utilization compared with total calcium monitoring.

In the absence of evidence to support routine iCa monitoring, we sought to characterize clinicians' ordering practices among several hospital internal medicine (HIM) services in a large academic medical center. We hypothesized that most iCa tests are ordered for routine monitoring in asymptomatic patients, and the results do not influence clinical decision making. As part of an ongoing quality-improvement project, this study's aims were twofold: 1) to assess the frequency of iCa measurements on our HIM services and 2) to assess the efficacy of an intervention based on clinician education to reduce the frequency of routine iCa monitoring.

METHODS

We retrospectively queried the laboratory database to identify the first 100 consecutive patients admitted to 6 HIM services in the Mayo Clinic, Rochester, MN, during January 2012, for whom an iCa test was ordered at any time during their inpatient episode. These 6 HIM services are staffed by physician assistants, nurse practitioners, and hospitalists. Using the electronic medical record (EMR), we identified the individual clinicians and departments responsible for ordering the iCa test. For example, a patient admitted to an HIM service may have an iCa test ordered as part of an Emergency Department (ED) or ICU evaluation. We also considered the possibility that the iCa test was ordered before a handoff of care (eg, routine morning laboratory tests ordered before a patient transfers from the ICU to an HIM service).

Two authors (DBN, KCS) reviewed all cases involving an iCa result originating from an HIM service. We reviewed...
the EMR looking for explicit comments by the HIM clinicians regarding the iCa indication. If no such comment was recorded in the HIM admission or progress notes, the EMR was then reviewed for active or historic medical conditions that might warrant iCa assessment (see Sidebar: Clinical Scenarios Generally Regarded to Warrant Ionized Calcium Monitoring) on the basis of available data and expert clinical opinion. In situations where the indication for ordering an iCa test was in question, the two authors jointly reviewed the record to determine the indication. If a medical indication for iCa monitoring was not found, we considered this to be “inappropriate” ordering. We then quantitatively the total number of iCa measurements and categorized them according to ordering department. We documented the ordering patterns in the ED and ICUs, but no intervention was performed in these departments and we did not interact with those groups.

A root-cause analysis indicated that lack of clinician awareness regarding the indications of iCa testing was the most significant factor likely contributing to the problem. Therefore, an educational intervention was undertaken consisting of a ten-minute presentation in February 2012 at a monthly HIM division meeting outlining the purpose of the quality-improvement project, the patient charge and additional laboratory resource utilization of iCa vs total calcium measurement, and the clinical scenarios generally regarded to warrant iCa measurement (see Sidebar: Clinical Scenarios Generally Regarded to Warrant Ionized Calcium Monitoring). The HIM division meeting is attended by HIM consultants, HIM fellows, nurse practitioners, and physician assistants. In addition, we identified the individual clinicians with the most frequent iCa test orders and provided additional discussion and one-on-one feedback.

To assess the effect of the intervention, we conducted another sampling of the first 100 consecutive patients admitted to HIM services during November 2012. We again sought to identify the ordering department and individual clinician responsible for the iCa test order. The primary outcome was the percentage difference of iCa test orders originated from the HIM services under investigation before and after the educational intervention. A χ² test was used to assess the change in proportion of iCa tests ordered by HIM clinicians before and after the intervention. As in the preintervention sample, the appropriateness of iCa testing was examined by review of the medical record using the indications listed in the Sidebar: Clinical Scenarios Generally Regarded to Warrant Ionized Calcium Monitoring.

RESULTS

The results of the Mayo Clinic laboratory database search are shown in Table 1. The included HIM services were responsible for 38 (38%) of the total 100 iCa tests ordered, with the remainder originating from the ED (29%), ICU (28%), and miscellaneous departments (5%). Following the educational intervention, the HIM services were responsible for 13% of iCa test orders, which amounted to a 66% reduction (p = 0.0007). Among HIM clinicians, consultants were responsible for 78% (n = 30) and 54% (n = 7), and midlevel clinicians were responsible for 22% (n = 8) and 46% (n = 6) of iCa test orders before and after the intervention, respectively.

In none of the HIM test-ordering instances was there any documentation for the rationale of iCa testing. The review of the EMR showed that iCa testing was appropriate only in 1 instance of 38 (3%) before the intervention and in 1 instance of 13 (8%) after the intervention.

DISCUSSION

Our data indicate that simple educational interventions along with targeted clinician feedback regarding effective test utilization can alter clinicians’ ordering patterns to reduce inappropriate and costly laboratory testing in a sustained manner. These interventions are inexpensive and provide an educational opportunity for improved patient care.

We found a surprisingly high number of iCa measurements among our HIM services despite a limited number of clinical scenarios that warrant direct measurement of iCa as well as an absence of data to support parenteral replacement in patients without signs or symptoms attributable to hypocalcemia. Ideally, the results of diagnostic testing should guide further diagnostic testing and therapeutic interventions with the potential to improve patient outcomes. However, there is a paucity of diagnostic tests with such characteristics in clinical medicine.

The rationale for iCa testing was not documented in the admission record or progress notes for any order originating

<table>
<thead>
<tr>
<th>Clinical Scenarios Generally Regarded to Warrant Ionized Calcium Monitoring</th>
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<tbody>
<tr>
<td>• Hypoparathyroidism following thyroidectomy</td>
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<tr>
<td>• Chelation after plasmapheresis or transfusion with citrated blood</td>
</tr>
<tr>
<td>• Severe pancreatitis</td>
</tr>
<tr>
<td>• Severe sepsis</td>
</tr>
<tr>
<td>• Severe metabolic alkalosis (pH &gt; 7.5) and acidosis (pH &lt; 7.3)</td>
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<tr>
<td>• Renal replacement therapy with a citrate dialysis bath</td>
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<tr>
<td>• Cardiac dysfunction associated with new or worsening left ventricular systolic function, prolonged QTc, and/or ventricular arrhythmias</td>
</tr>
<tr>
<td>• Administration of drugs associated with hypocalcemia: mithramycin (also known as plicamycin), bisphosphonates, calcitonin, and oral or parenteral phosphate preparations</td>
</tr>
<tr>
<td>• Administration of chemotherapeutic agents associated with hypocalcemia: cisplatinum, combined use of 5-fluorouracil, and leucovorin</td>
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<table>
<thead>
<tr>
<th>Table 1. Ionized calcium tests ordered before and after the intervention</th>
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<tbody>
<tr>
<td>Ordering department</td>
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<tr>
<td>Hospital internal medicine</td>
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<tr>
<td>Intensive care units</td>
</tr>
<tr>
<td>Emergency Department</td>
</tr>
<tr>
<td>Other</td>
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</table>
from an HIM service. We would therefore assume that the indication for iCa measurement originating from the included HIM services was, overwhelmingly, for routine monitoring. We also hypothesize that most iCa test orders originating from the ED and ICUs were also for routine monitoring; however, this would require further research to clarify.

Tantamount to a paucity of outcomes data on parenteral calcium supplementation in critical or noncritical illness, iCa measurement is more costly than total calcium measurement. However, besides the cost difference, one also must consider the additional complexities of iCa measurement, including handling and transport, the laboratory equipment calibrated and devoted to iCa measurement, and the additional personnel required to maintain and to calibrate the equipment.

There are some weaknesses of the present study warranting discussion. First, the possibility exists that we may have overestimated or underestimated the effect of our intervention because of an error of omission. To minimize this possibility, we generated samplings of 100 consecutive iCa measurements to form our case populations. In this way, errors of omission resulting from an incomplete study population would be distributed by chance equally across all sampled subgroups (HIM, ED, ICUs, miscellaneous ordering departments). Additionally, we recognize that this is a convenience sample, and the lack of matching between preintervention and postintervention study populations might lead to potential biases and confounders that limit the strength of the conclusions. Last, educational interventions are known to have limited durability. It is unknown how durable the effect of our intervention will be beyond the 10 months of our follow-up assessment, and this remains to be determined.

**CONCLUSION**

Herein, we presented the results of a simple intervention based on clinician education and feedback to reduce the frequency of unnecessary routine iCa measurement. We were able to decrease routine iCa measurement by 66% (p = 0.0007) in participating HIM services. Even though unnecessary ordering was not eliminated, this reduction translates to cost savings and improved use of resources. Laboratory testing that is driven by clinical indication can improve the cost-effectiveness of daily clinical practice. In the current era of unprecedented challenges in health care systems worldwide, efforts to optimize the use of available resources should be encouraged. Simple educational interventions aiming at the elimination of ordering practices that are potentially harmful to patients and costly can be effective.

**Disclosure Statement**

Dr Jaffe is a consultant for Bechman, Ortho, Alere, Abbott, Critical DX, Radiometer, Roche, Trinity, ET Healthcare, the American Heart Association, and Amgen. The author(s) report no other conflicts of interest to disclose.

**Acknowledgment**

Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

**References**


**Destroy the Reason**

**Medicine** [is] the only profession that labours incessantly to destroy the reason for its own existence.

— James Bryce, Viscount Bryce of Dechmont, 1838-1922, British academic, jurist, historian, and Liberal politician
Temporal Comorbidity of Mental Disorder and Ulcerative Colitis

David Cawthorpe, PhD; Marta Davidson, MD

ABSTRACT

Objectives: Ulcerative colitis is an inflammatory bowel disease that rarely exists in isolation in affected patients. We examined the association of ulcerative colitis and International Classification of Diseases mental disorder, as well as the temporal comorbidity of three broad International Classification of Diseases groupings of mental disorders in patients with ulcerative colitis to determine if mental disorder is more likely to occur before or after ulcerative colitis.

Methods: We used physician diagnoses from the regional health zone of Calgary, Alberta, for patient visits from fiscal years 1994 to 2009 for treatment of any presenting concern in that Calgary health zone (763,449 patients) to identify 5113 patients age younger than 1 year to age 92 years (2120 males, average age = 47 years; 2993 females, average age = 48 years) with a diagnosis of ulcerative colitis.

Results: The 16-year cumulative prevalence of ulcerative colitis was 0.0058%, or 58 cases per 10,000 persons (95% confidence interval = 56-60 per 10,000). Although the cumulative prevalence of mental disorder in the overall sample was 5390 per 10,000 (53.9%), we found that 4192 patients with ulcerative colitis (82%) also had a diagnosis of a mental disorder. By annual rate of ulcerative colitis, patients with mental disorder had a significantly higher annual prevalence. The mental disorder grouping neuroses/depressive disorders was most likely to arise before ulcerative colitis (odds ratio = 1.87 for males; 2.24 for females).

Conclusions: A temporal association was observed between specific groups of International Classification of Diseases mental disorder and ulcerative colitis, indicating a possible etiologic relationship between the disorders or their treatments, or both.

INTRODUCTION

Ulcerative colitis is a form of inflammatory bowel disease (IBD) characterized by inflammation of the colonic mucosa. Inflammation typically begins in the rectum and spreads proximally through the colon in a continuous manner. The hallmark clinical features of ulcerative colitis are recurrent flares associated with painful, bloody diarrhea followed by spontaneous remission. During acute flares, severe inflammation can lead to major complications, such as blood loss and toxic megacolon.

The pathogenesis of ulcerative colitis is poorly understood and represents a complex interaction between heredity, immune dysregulation, and environment. Ulcerative colitis is a disease with an annual incidence ranging from 6.3 to 24.3 per 100,000 person-years that is higher in industrialized nations. A Western lifestyle and environment appear to be risk factors for ulcerative colitis because of its emergence in nations undergoing industrialization.

Diagnosis, prognostication, and treatment planning necessitate endoscopic and histologic studies. The degree of inflammation and extent of disease guide therapy, which is to first induce remission and then maintain remission. Whereas the treatment paradigms for ulcerative colitis have substantially changed with the advent of biologic therapy, subgroups of affected patients fail to respond or lose treatment response, presenting challenges in disease management. A recent review identifies a range of clinical factors to consider as an empirical rationale for modifying treatment. Factors determining the variability in response to treatment are likely manifold, including individual differences in genetics, environment, and immune dysregulation. Moreover, as ulcerative colitis is a chronic disease with long survival rates, the potential cannot be ignored for comorbidities to interact with and to complicate the ulcerative colitis vulnerability, disease processes, and treatment.

Román and Muñoz reviewed the comorbidities associated with IBD, including mental disorder. The authors pointed out that affective disorders have been extensively studied in patients with IBD, whereas data on conditions such as psychoses and other mental disorders are scarce. Recently, a standard systematic review protocol was established to investigate the putative linkage between IBD and psychological factors, which, although suspected, has not been established. This protocol was developed largely as a response to previous reviews concerned with this link that had conceptual and methodologic limitations. Although the proposed protocol is comprehensive, it has not yet been implemented, in part because of the extensive reliance on the assimilation of high-quality research. In the meantime, informatics approaches may provide additional insights relevant to the understanding of the relationship of not just psychological factors but also other somatic and biologic factors of ulcerative colitis.

In this study, we focused on the diagnosis of ulcerative colitis, recognizing that it rarely exists in isolation but is rather part of a complex matrix of disorders arising in patients over time. We examined three main groupings of mental disorder, composed of specific ranges of mental disorder codes in the International Classification of Diseases (ICD),...
to illustrate the temporal relationship with ulcerative colitis on the basis of the index (first occurrence) diagnosis of mental disorder and ulcerative colitis. This article is the first, to our knowledge, to describe the prevalence and temporal comorbidity of mental disorder and ulcerative colitis as it arises in affected individuals in a population. The examined relationship between ulcerative colitis and mental disorder in a regional population in Canada provides additional insight into the etiology of ulcerative colitis.

METHODS

With use of a population-based sampling frame, 763,449 patients (45.8% male) were selected from the regional health service registry (Calgary, Alberta, Canada) and merged with all direct physician billings from 1993 to 2010 for treatment of any presenting concern. Each billing record pertains to services rendered to patients on specified dates resulting in assignment of an ICD (Version 9) diagnostic code. This study employed anonymous data that included ICD diagnoses, visit date, age at index visit, and sex.

The overall cumulative 16-year prevalence and the annual prevalence rates were, respectively, based on the number of unique patients in whom a physician diagnosed ulcerative colitis in the overall 16-year sample and in any given year, denominated by the civic census from 1994 to 2009. These years represent the interval having full fiscal years for which data were available. Unique implies that each patient was counted only once in a given period. Preliminary analysis indicated male-female differences in rates; hence, further analyses included stratification on the basis of sex to control for this effect.

The data were collapsed into 2 basic groups representing the presence or absence of ulcerative colitis. All psychiatric diagnoses (ICD Codes 290-319) were collapsed into 3 general groupings on the basis of the presence or absence of specific ranges of the following mental disorders: psychotic disorders (Codes 290-299), not including major depression; neuroses/depressive disorders, a group including anxiety disorders; as well as major depression and depressive disorders (ie, Codes 296.2, 296.3, 300, 308, 309, 311); and a group consisting of all other mental disorders (all remaining ICD mental disorder codes). The data were stratified further on the basis of the temporal occurrence of the index diagnoses of either mental disorder or ulcerative colitis. The 3 cases in which both diagnoses were assigned on the same day were assigned to the group “mental disorder after ulcerative colitis.”

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated on the basis of individual counts in each cell using the stratifications noted earlier. Criteria related to group classification of the data were developed to ensure that the 3 psychiatric groupings were independent. Analyses of rates and ORs were based on comparison of overlapping and nonoverlapping 95% CIs. For rates, significant statistical differences between proportions in any given year were estimated by comparison of the 95% CIs using the standard formula, wherein nonoverlapping 95% CIs represent significant differences (p < 0.05, with Z set to 1.96) and overlapping 95% CIs indicate statistical nonsignificance.

On the basis of the index (first) diagnosis date among those with ulcerative colitis and three groupings of mental disorder, two time-based groups were identified regarding whether mental disorder arose before or after ulcerative colitis. The main comparisons within groups of mental disorder and ulcerative colitis were based on the temporal order of each of the three mental disorder groupings being associated with ulcerative colitis, as represented by ORs. The ORs were independent of the temporal order and examined only the likelihood in independent mental disorder groups of arising either before or after ulcerative colitis. Therefore, the hypothesis was constructed on the assumption that the respective ORs in mental disorder groups, arising either before or after ulcerative colitis, would be significantly different from one another. Between-mental disorder group comparisons provided an indication of mental disorder group similarity or differences in magnitude and direction of the relationship.

RESULTS

In the dataset there were 5113 patients ranging in age from younger than 1 year to 92 years old (2120 males, mean

Table 1. Ulcerative colitis regional population rates (per 10,000) by sex with or without mental disorder, 1994-2009

<table>
<thead>
<tr>
<th>Year</th>
<th>Males (95% CI)</th>
<th>Females (95% CI)</th>
<th>Total rate* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No mental disorder</td>
<td>Mental disorder</td>
<td>No mental disorder</td>
</tr>
<tr>
<td>1994</td>
<td>6 (5-7)</td>
<td>28 (26-30)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>1995</td>
<td>7 (6-8)</td>
<td>30 (28-32)</td>
<td>5 (4-6)</td>
</tr>
<tr>
<td>1996</td>
<td>7 (6-8)</td>
<td>30 (28-32)</td>
<td>5 (4-6)</td>
</tr>
<tr>
<td>1997</td>
<td>6 (5-7)</td>
<td>30 (28-32)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>1998</td>
<td>7 (6-8)</td>
<td>29 (27-31)</td>
<td>5 (4-6)</td>
</tr>
<tr>
<td>1999</td>
<td>6 (5-7)</td>
<td>29 (27-31)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>2000</td>
<td>6 (5-7)</td>
<td>28 (26-30)</td>
<td>5 (4-6)</td>
</tr>
<tr>
<td>2001</td>
<td>6 (5-7)</td>
<td>28 (26-30)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>2002</td>
<td>6 (5-7)</td>
<td>28 (26-30)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>2003</td>
<td>6 (5-7)</td>
<td>26 (25-27)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>2004</td>
<td>6 (5-7)</td>
<td>27 (26-28)</td>
<td>6 (5-7)</td>
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<tr>
<td>2005</td>
<td>6 (5-7)</td>
<td>27 (26-28)</td>
<td>6 (5-7)</td>
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<tr>
<td>2006</td>
<td>6 (5-7)</td>
<td>26 (25-27)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>2007</td>
<td>6 (5-7)</td>
<td>24 (23-25)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>2008</td>
<td>6 (5-7)</td>
<td>23 (22-24)</td>
<td>6 (5-7)</td>
</tr>
<tr>
<td>2009</td>
<td>6 (5-7)</td>
<td>22 (21-23)</td>
<td>5 (4-6)</td>
</tr>
</tbody>
</table>

* Males and females combined with and without mental disorder. CI = confidence interval.
The 16-year cumulative prevalence rate for ulcerative colitis was 58 per 10,000 (95% CI = 56-60). Table 1 shows the annual population rates in the health region for ulcerative colitis for males and females with and without mental disorder. Comparison of the CIs indicates that for both sexes having any mental disorder significantly increases the rate of ulcerative colitis in each year. Furthermore, although there was no apparent difference in the CIs of either sex without a mental disorder, female rates by year were significantly higher than those observed for males.

In the groups with no mental disorder, the rates of ulcerative colitis remained stable, whereas those for males and females having any mental disorder peaked in 1996 and significantly decreased in subsequent years, as demonstrated by a comparison of nonoverlapping CIs.

Table 2 presents the data on which the ORs and CIs in Table 3 were calculated. The groups representing mental disorder occurring in time before or after ulcerative colitis are independent within each strata (eg, psychotic disorders; neuroses/depressive disorders; and other disorders, which included all other ICD diagnoses). For each grouping of mental disorders, the OR compared the presence or absence of mental disorder given the presence or absence of ulcerative colitis.

In Table 3, comparison of the CIs of the ORs indicated that unlike psychotic disorders, neuroses/depressive disorders as a group of mental disorders were significantly more likely to occur before ulcerative colitis for both males and females. Other mental disorders as a group were significantly more likely to arise before ulcerative colitis for females. However, for males, only other mental disorders were significantly less likely to arise after ulcerative colitis. Neuroses/depressive disorders were most likely to arise before ulcerative colitis for both sexes.

## DISCUSSION

Ulcerative colitis is an inflammatory disease of the rectum and colon causing substantial morbidity. Although the exact etiology of ulcerative colitis remains unknown, a combination of genetic predisposition and environmental risk factors underlie its pathogenesis. Unlike the findings from our study, Molodecky et al found that ulcerative colitis appears to be on the rise around the globe. Ulcerative colitis is more prevalent in developed nations, with the highest prevalence in Europe (51 per 10,000 persons) and North America (25 per 10,000 persons).

Consistent with these data, the annual overall prevalence of ulcerative colitis, inferred from physician diagnosis, in the Calgary health zone was highest in 1996 (40 per 10,000) and steadily decreased to 30 per 10,000 in 2009. Whereas the annual prevalence was the same for males and females among those without any mental disorder, with a maximum of 7 per 10,000, the annual prevalence was much higher for those with any mental disorder, with males

### Table 2. Count of patients by sex in each diagnostic grouping by mental disorder and ulcerative colitis

<table>
<thead>
<tr>
<th>Sex</th>
<th>Temporal order of mental disorder</th>
<th>Mental disorder group</th>
<th>No ulcerative colitis, no mental disorder</th>
<th>Ulcerative colitis, no mental disorder</th>
<th>No ulcerative colitis, mental disorder</th>
<th>Ulcerative colitis, mental disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Before ulcerative colitis</td>
<td>Psychotic disorders</td>
<td>369,555</td>
<td>2432</td>
<td>41,755</td>
<td>262</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other disorders</td>
<td>293,728</td>
<td>1645</td>
<td>117,582</td>
<td>864</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroses/depression</td>
<td>167,486</td>
<td>547</td>
<td>243,824</td>
<td>1787</td>
</tr>
<tr>
<td>Male</td>
<td>Before ulcerative colitis</td>
<td>Psychotic disorders</td>
<td>316,586</td>
<td>1798</td>
<td>30,440</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other disorders</td>
<td>242,660</td>
<td>1201</td>
<td>104,366</td>
<td>548</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroses/depression</td>
<td>203,633</td>
<td>695</td>
<td>143,393</td>
<td>917</td>
</tr>
<tr>
<td></td>
<td>After ulcerative colitis</td>
<td>Psychotic disorders</td>
<td>316,586</td>
<td>1798</td>
<td>30,440</td>
<td>180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other disorders</td>
<td>242,660</td>
<td>1201</td>
<td>104,366</td>
<td>548</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroses/depression</td>
<td>203,633</td>
<td>695</td>
<td>143,393</td>
<td>917</td>
</tr>
</tbody>
</table>
and females having maximum annual prevalence rates of 30 per 10,000 and 52 per 10,000, respectively. The 16-year cumulative prevalence in the population was 58 per 10,000, which is in keeping with the rates observed in Europe. Even though the overall rates are comparable, the reduction observed in the annual prevalence over time in ulcerative colitis for those with mental disorder and the constant rate in those with no mental disorder was opposite to the increases reported in the literature. As with the range of rates reported in the literature, differences in the methods, data sources, and diagnostic precision may account for different findings.

We found that a significant portion of patients with ulcerative colitis also had mental disorder. Preliminary evidence indicates a link between inflammation and a subset of mental disorder, namely mood disorders. A recent study quantified this association by showing that hospitalization for infection and autoimmune disease increased the risk of a mood disorder developing by 62% and 45%, respectively. In this study, there were distinct patterns of mental disorder that preceded and followed ulcerative colitis, principally the ICD group consisting of neuroses and depressive disorders. This study most closely resembles that of Kurina et al., who examined the temporal relationship of depression in patients with IBD. Groups were also distinguished in terms of depression arising either before or after bowel disorder, being either etiologic or consequential. The present study extends these results in terms of describing the broad yet temporally distinct groups of mental disorder diagnosed in association with ulcerative colitis in a population.

Presently, there is no satisfactory explanation for the observed patterns of mental disorder and ulcerative colitis. Future research is required to examine this observation in more detail. One possibility is the effect on inflammation and the autoimmune response of psychotropic medications used to treat anxiety and depression, a mechanism that may play a role in the etiology of ulcerative colitis and a hitherto unexamined, long-term risk of long-term medication use. We hope to examine this relationship specifically in relation to anxiety, autoimmune disorders, and ulcerative colitis.

It is not surprising to find that certain mental disorders occur either before or after ulcerative colitis, given that ulcerative colitis has a peak incidence between the second and fourth decades of life. Disorders such as those specifically diagnosed in early childhood would naturally arise before ulcerative colitis. Likewise, a mental disorder such as dementia associated with functional decline later in life would naturally be expected to occur, on average, after a diagnosis of ulcerative colitis. Further analysis on the basis of inclusion and exclusion of age-related disorder stratifications is warranted. The explanation for the observed temporal relationship between mental disorder and ulcerative colitis based on confounding by age, in which the natural histories of the various disorders manifest themselves at different ages, is feasible. However, the presence of distinct patterns of specific groups of disorders arising before or after ulcerative colitis may also point to a common underlying genetic vulnerability. Moreover, if random processes underpinned the observed temporal profiles of mental disorders arising either before or after ulcerative colitis, one would not expect such substantial differences in the time between onset of specific mental disorder preceding or following ulcerative colitis. More detailed examination of the temporal precedence of mental disorders in those with ulcerative colitis is indicated given the overrepresentation of mental disorder in the ulcerative colitis group (81%) compared with the general population (53.9%).

Limitations

The diagnostic groupings combined diagnoses into two relatively coherent ICD diagnostic groupings (psychotic disorders and neuroses/depressive disorders) on the basis of more common pharmacologic treatments, as well as one more heterogenous catchall grouping (other). Although the groupings provided a “broad-stroke” approach to examination of the relationship between ulcerative colitis and mental disorder, given the overrepresentation of mental disorder among those with ulcerative colitis, more specific diagnosis-related associations may well be masked. For example, that psychoses were found not to have any temporal relationship with ulcerative colitis does not mean that there are not psychotic disorders that, when studied individually, may be discovered to have similar effects. Ultimately, a detailed analysis of all diagnoses is warranted.

Another study limitation is the precision (reliability and validity) of physician diagnosis. Lack of precision affects all research that is based on diagnosis at some level in terms of false-positive

### Table 3. Odds ratios of mental disorder groups given before and after ulcerative colitis by sex and temporal occurrence of ulcerative colitis

<table>
<thead>
<tr>
<th>Sex</th>
<th>Temporal order of mental disorder</th>
<th>Mental disorder group</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>Before ulcerative colitis</td>
<td>Psychotic disorders</td>
<td>0.95 (0.84-1.08)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other disorders</td>
<td>1.31 (1.21-1.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroses/depression*</td>
<td>2.24 (2.04-2.47)</td>
</tr>
<tr>
<td></td>
<td>After ulcerative colitis</td>
<td>Psychotic disorders</td>
<td>1.09 (0.96-1.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other disorders</td>
<td>0.73 (0.66-0.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroses/depression*</td>
<td>0.83 (0.74-0.93)</td>
</tr>
<tr>
<td>Male</td>
<td>Before ulcerative colitis</td>
<td>Psychotic disorders</td>
<td>0.82 (0.69-0.97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other disorders</td>
<td>1.06 (0.96-1.17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroses/depression*</td>
<td>1.87 (1.7-2.07)</td>
</tr>
<tr>
<td></td>
<td>After ulcerative colitis</td>
<td>Psychotic disorders</td>
<td>1.04 (0.89-1.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other disorders</td>
<td>0.72 (0.64-0.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuroses/depression*</td>
<td>1.04 (0.93-1.16)</td>
</tr>
</tbody>
</table>

* p < 0.05
CI = confidence interval.
and false-negative rates of diagnosis. One could assume that each category or diagnosis suffers more or less equally from this problem to the extent that one could expect a random distribution of more or less accurate diagnoses based on physician expertise.

Finally, for simplicity, only the specific ICD diagnosis of ulcerative colitis was considered in this study. Other related bowel diseases, such as Crohn disease, were not included in the grouping. The relationship between a wider grouping of bowel diseases and the mental disorder groupings remains unknown. Also unknown is the degree to which ulcerative colitis or mental disorder is overrepresented in other disorders or whether other disorders are overrepresented in ulcerative colitis more than mental disorder.

Future Directions

The present study examined the relation of three broad groups of mental disorder and ulcerative colitis in the temporal order of the mental disorder group occurring before or after ulcerative colitis. Although neurotic and depressive disorders were shown to have a statistically and epidemiologically significant temporal relationship with the onset of ulcerative colitis, the disorders accounting for this effect were not identified specifically. As such, the present study points to a novel direction, which will guide further research and education, rather than a conclusive exposition of clinical fact that may be translated into practice.

Understanding of ulcerative colitis is well developed in current clinical and diagnostic knowledge, with new treatment options for this condition having been identified. However, there has been little description of the profile of disorders associated with ulcerative colitis. The present article describes the relationship of specific mental disorder groups that arise in temporal association with ulcerative colitis. Of note is that mental disorder represents 1 main class of ICD disorders among 18 main ICD classes in total.

The challenge to future research lies in the difficulty of representing the spatial and temporal complexity of how disorders emerge in patients across time. Additionally, ulcerative colitis is one dependent variable in a collection of disorders related to a much broader class of disorders affecting not only the bowel but the entire digestive system. Yet, the approach to understanding the etiologic and prognostic effect of comorbidity on ulcerative colitis tends to focus on individual disorders or small clusters of similar disorders. Common symptoms underpin our understanding of ulcerative colitis and related diseases in addition to our evolving understanding of the biochemical and genetic substrates and mechanisms giving rise to disease. It is apparent from the present study that there is useful information embedded in the diagnostic profiles of clinical populations.

The present example of population-based diagnostic analysis represents a novel approach to organize thinking about the relationship between diagnostic classifications for how patterns of diagnosis emerge in populations over time. Information emerging from this approach challenges traditional thinking about disease processes and may actually influence the organization of health services designed to treat specific disorders in clinical pathways. The present research is in some ways similar to the recently identified epistemologic threat to the validity of medical knowledge that is based on how medical research is designed and implemented. The profile of mental disorder associated with ulcerative colitis represents a complex yet virtually unexamined source of influence on treatment effect. Studies are most often limited to the examination of one or two associated clinical conditions. Using the present dataset, we have the opportunity to coherently examine and rank the associations in time of ulcerative colitis and all disorders.

Evidence suggests that serotonin reuptake inhibitors may play a role in immune dysregulation. Although this evidence has not been explicitly studied in relationship to the etiology of ulcerative colitis, the present findings suggest that there may be a link, given that most anxiety and depressive disorders have been treated with oral serotonin reuptake inhibitors. Hence, on the basis of the present findings, it is reasonable to postulate that future research may fruitfully focus on this putative link. Serotonin receptors are no doubt ubiquitous throughout the human body and may be involved in regulation of the immune response underpinning ulcerative colitis. This tenuous example serves to illustrate a main finding emerging from this approach to the analysis of diagnostic data. Regarding the etiology of ulcerative colitis, the pharmaco logic treatment of mental disorder and the mental disorder itself are confounded in terms of the putative effect on emergence of ulcerative colitis.

Finally, in our past population-based studies using this same dataset, we have provided validation of the adverse childhood experiences study. In those studies the main assumption was that early adversity is one gateway to mental disorder in later life, and we demonstrated a clear relationship between mental disorder and biomedical or somatic disorders. More importantly, additional studies have drawn associations between somatic disorders, specifically ulcerative colitis and early adversity. Use of our current, novel approach to expand analysis of the temporal comorbidity of mental disorder and specific biomedical and somatic disorders may help to extend understanding of the potentially confounding treatment and etiologic factors as these emerge over time in the complex relationship between experience and health status.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgments

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Kathleen Louden, ELS, of Louden Health Communications provided editorial assistance.

References


Disease

We are accustomed to speak of “disease entities” as though they had an independent, individual existence and could be recognized as friends—or better, perhaps, as enemies. This is … one of those abstractions that do violence to the reality of the … situation, for there is no disease aside from the patient. The disease is the change produced in the patient by the pathological process. Diagnosis involves the observation of the patient as he is, and … a reconstruction in imagination of the patient as he was, before afflicted. The disease is the difference between those two pictures.

— Glomerular Nephritis, Thomas Addis, 1881-1949, English physician-scientist and pioneer in the field of nephrology
High Amount of Dietary Fiber Not Harmful But Favorable for Crohn Disease

Mitsuro Chiba, MD, PhD; Tsuyotoshi Tsuji, MD, PhD; Kunio Nakane, MD, PhD; Masafumi Komatsu, MD, PhD

ABSTRACT

Current chronic diseases are a reflection of the westernized diet that features a decreased consumption of dietary fiber. Indigestible dietary fiber is metabolized by gut bacteria, including Faecalibacterium prausnitzii, to butyrate, which has a critical role in colonic homeostasis owing to a variety of functions. Dietary fiber intake has been significantly inversely associated with the risk of chronic diseases. Crohn disease (CD) is not an exception. However, even authors who reported the inverse association between dietary fiber and a risk of CD made no recommendation of dietary fiber intake to CD patients. Some correspondence was against advocating high fiber intake in CD.

We initiated a semivegetarian diet (SVD), namely a lacto-ovo-vegetarian diet, for patients with inflammatory bowel disease. Our SVD contains 32.4 g of dietary fiber in 2000 kcal. There was no untoward effect of the SVD. The remission rate with combined infliximab and SVD for newly diagnosed CD patients was 100%. Maintenance of remission on SVD without scheduled maintenance therapy with biologic drugs was 92% at 2 years. These excellent short- and long-term results can be explained partly by SVD. The fecal bacterial count of F prausnitzii in patients with CD is significantly lower than in healthy controls. Diet reviews recommend plant-based diets to treat and to prevent a variety of chronic diseases. SVD belongs to plant-based diets that inevitably contain considerable amounts of dietary fiber. Our clinical experience and available data provide a rationale to recommend a high fiber intake to treat CD.

INTRODUCTION

There are interesting articles published on Crohn disease (CD) and dietary fiber.1-3 The cohort study by Ananthakrishnan et al1 showed that a long-term intake of dietary fiber was associated with a lower risk of CD. The authors of the study and its editorial2 advocated to the public the consumption of a recommended amount of dietary fiber (25 g/day for women and 38 g/day for men) (Table 1). However, there was no statement regarding CD patients.1,2 Stein and Cohen3 were against advocating high fiber intake in CD without any clear reason. This misleads physicians and patients into continuance of the conventional low-residue diet for CD. Our clinical experience and available data favor the recommendation of a high fiber diet for CD.

DIETARY FIBER IN HEALTH AND DISEASE

Effect of Dietary Fiber

Dietary fiber is known to 1) improve laxation by increasing bulk and reducing transit time of feces through the bowel; 2) increase excretion of bile acid, estrogen, and fecal procarcinogens and carcinogens by binding to them; 3) lower serum cholesterol; 4) slow glucose absorption and improve insulin sensitivity; 5) lower blood pressure; 6) promote weight loss; 7) inhibit lipid peroxidation; and 8) provide anti-inflammatory properties (Figure 1).4 After a large prospective cohort study, Park et al4 found that dietary fiber intake was significantly inversely associated with risk of total death and death from cardiovascular disease, infectious diseases, and respiratory diseases in both men and women. Dietary fiber intake was also related to a lower risk of death from cancer in men (Figure 1). Among specific sources of dietary fiber, fiber from grains showed the most consistent inverse association with risk of total and cause-specific death. Namely, current chronic diseases are related to decreased consumption of dietary fiber—which is a part of dietary Westernization.5 In evaluating the effects of dietary Westernization we are apt to stress adverse effects of increased consumption of animal protein or animal fat, but it is equally important to stress the drawbacks of decreased consumption of dietary fiber.

Mechanism of the Effect of Dietary Fiber through the Gut Microflora

Our understanding of the mechanisms of the effect of dietary fiber has advanced since Burkitt et al6 on the basis of epidemiologic data, postulated that the high incidence of colon cancer, diverticulosis, irritable bowel syndrome, and hemorrhoids as well as atherosclerosis, coronary artery disease, diabetes, obesity, and hyperlipidemia is secondary to prolonged
High Amount of Dietary Fiber Not Harmful But Favorable for Crohn Disease

Indigestible dietary fiber is metabolized to short-chain fatty acids, primarily acetate, propionate, and butyrate, by gut bacteria. Short-chain fatty acids serve as a major energy source for colonocytes. Among short-chain fatty acids, butyrate has a critical role in colonic homeostasis owing to a variety of functions: inhibiting inflammation and carcinogenesis, reinforcing various components of the colonic defense barrier, decreasing oxidative stress, and providing a satiety sensation. These beneficial effects overlap naturally with those of dietary fiber (Figure 1). Therefore, it is reasonable to postulate a sequence of shortage of dietary fiber, decreased butyrate, and loss of homeostasis that leads to chronic diseases (Figure 1). Recent observations that gut microflora is formed by diet and an introduction of the concept that gut microflora is an environmental factor in obesity studies underline the critical role of diet.  

*Faecalibacterium prausnitzii* is one of the most abundant commensal bacteria in the human intestinal microflora of healthy adults, representing more than 5% of the total bacterial population. *F prausnitzii* is known to produce butyrate, and its production is associated with dietary fiber. A meta-analysis shows that the fecal bacterial count of *F prausnitzii* in patients with inflammatory bowel disease (IBD) is significantly lower than in healthy controls, particularly in CD (Figure 1). Whether this finding is observed even before treatment for IBD or whether it is a secondary effect of the current low-residue diet in IBD is to be elucidated.

### DIETARY FIBER AND CROHN DISEASE Case Control Study

Three studies described by Hou et al. on pre-illness dietary fiber consumption and CD showed that high fiber intake decreased CD risk. One study showed statistical significance in those consuming more than 22.1 g/day compared with less than 13.8 g/day (odds ratio, 0.12; 95% confidence interval, 0.04-0.37).

### Cohort Study

The cohort study by Ananthakrishnan et al., in which 170,776 women in the Nurses’ Health Study were followed up for 26 years, found that the highest quintile for consuming dietary fiber (median, 24.0 g/day) was associated with a 40% reduction in risk of CD compared with the lowest quintile (11.6 g/day) (Table 1). This was the first prospective cohort study on a large scale determining

<table>
<thead>
<tr>
<th>Reference</th>
<th>Subject</th>
<th>Diet</th>
<th>Amount of dietary fiber</th>
<th>Efficacy for CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ananthakrishnan et al, 2013&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Nurses</td>
<td>The highest quintile of dietary fiber intake (median)</td>
<td>24.0 g/day</td>
<td>Decreased risk of CD</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The lowest quintile of dietary fiber intake (median)</td>
<td>11.6 g/day</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Heaton et al, 1979&lt;sup&gt;15&lt;/sup&gt;</td>
<td>Patients with CD</td>
<td>An unrefined-carbohydrate, fiber-rich diet</td>
<td>33.4 ± 1.8 g/day</td>
<td>Decrease in admissions</td>
</tr>
<tr>
<td>Ritchie et al, 1987&lt;sup&gt;16&lt;/sup&gt;</td>
<td>Patients with CD</td>
<td>An unrefined-carbohydrate, fiber-rich diet (median at 2 years)</td>
<td>27.9 g/day</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>Control: a refined-carbohydrate diet (median at 2 years)</td>
<td></td>
<td>18.1 g/day</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Chiba et al, 2010&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Patients with CD</td>
<td>Semivegetarian diet (Soluble dietary fiber)</td>
<td>32.4 ± 2.1 g/2000 kcal/day</td>
<td>Relapse prevention</td>
</tr>
<tr>
<td></td>
<td>(Insoluble dietary fiber)</td>
<td></td>
<td>(6.8 ± 0.7 g/2000 kcal/day)</td>
<td></td>
</tr>
<tr>
<td>Kaplan, 2013&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Recommendation for women</td>
<td>Not applicable</td>
<td>25 g/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recommendation for men</td>
<td></td>
<td>38 g/day</td>
<td></td>
</tr>
<tr>
<td>Chiba et al, 2010&lt;sup&gt;18&lt;/sup&gt;</td>
<td>Recommendation for women</td>
<td>Not applicable</td>
<td>17 g/day</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recommendation for men</td>
<td></td>
<td>20 g/day</td>
<td></td>
</tr>
</tbody>
</table>

CD = Crohn disease.
the relationship between dietary fiber and the risk of CD. It was concluded that long-term intake of dietary fiber is associated with a lower risk of CD.

**Intervention Study**

There have been two dietary intervention studies in CD focusing on dietary fiber. Heaton et al.\(^\text{15}\) reported significant efficacy of an unrefined-carbohydrate, fiber-rich diet in CD compared with a control diet in the number of hospital admissions, the duration of hospitalizations, and total number of days in the hospital. In this study, dietary fiber was 33.4 ± 1.8 g/day (Table 1). However, a controlled multicenter trial by Ritchie et al.\(^\text{16}\) in 1987 was not able to reproduce the effect (Table 1). To our knowledge, there has been no subsequent intervention study focusing on dietary fiber. The above conflicting results seem to be because of the difference in subjects that happened while evaluating the maintenance effect of a concomitant elemental diet during infliximab therapy.\(^\text{17}\) The early use of infliximab is more effective than late use in CD, which seemed to result in the conflicting effects of an elemental diet. Most patients (69%) were newly diagnosed (within 3 months) in the study by Heaton et al.,\(^\text{15}\) whereas most patients (54%) were long-standing with intestinal resection in the study by Ritchie et al.\(^\text{16}\). Recently diagnosed cases might be more responsive to dietary manipulation than long-standing cases.

**METHODS AND RESULTS**

**Our Experience**

Expanding our knowledge in gut microflora led to the concept that the greatest environmental factor in IBD is diet-associated gut microflora.\(^\text{18}\) The microflora is disrupted in IBD mainly by a Westernized diet: increased consumption of animal fat, animal protein, and sugar as well as decreased consumption of dietary fiber. The conventional recommended diet for IBD is a low-residue diet that stems from a fear of irritating the bowel with dietary fiber. However, there is no evidence that such a diet is ideal for IBD.\(^\text{19}\) A low-residue diet that lacks nondigestible carbohydrates might accelerate the dysbiosis in IBD.\(^\text{19,20}\) Hoping to increase beneficial bacteria in the gut, we initiated a semivegetarian diet (SVD) replacing the low-residue diet.\(^\text{18}\) Our SVD is a lacto-ovo-vegetarian diet with an additional serving of fish once a week and meat once every 2 weeks. We provided SVD during hospitalization for 22 consecutive adult CD cases: 14 men and 8 women, age 19 to 77 years (median, 26.5 years), with enterocolitis (11), enteritis (1), or colitis (10). Seventeen patients had active CD whereas 5 patients had undergone resective surgery immediately before the intervention. With regard to the active CD patients, 12 were experiencing the initial onset and 5 were experiencing relapse, the median disease duration was 8.0 months (range, 1 to 74 months), and the main medication was standard induction therapy with infliximab in 16 patients and sulfasalazine in 1. SVD was initiated on the same day as infusion of infliximab. With regard to the postoperative CD patients, 1 was experiencing initial onset with 2 years of disease duration and 4 were experiencing relapse with disease duration more than 8 years; the intervention began on postoperative day 12 to 25; and the main medication was metronidazole 750 mg/day. Initially approximately 800 or 1100 kcal/day was given, and calories were gradually increased to a maximum of approximately 30 kcal/kg standard body weight. The median length of SVD was 49 days for those with active CD and approximately 3 weeks for those with postoperative CD. Remission was defined as the disappearance of active symptoms of CD. All active CD patients obtained remission: the CD active index significantly decreased from 255 ± 169 (mean ± SD) on admission to 46 ± 24 at week 6 (p < 0.0001).

Those patients who achieved clinical remission, either medically or surgically, were provided dietary guidance for SVD before discharge and were advised to maintain SVD after discharge. None of the patients took infliximab or immunosuppressants in the follow-up study. Our SVD contains 32.4 ± 2.1 g of dietary fiber (soluble dietary fiber, 6.8 ± 0.7 g; insoluble dietary fiber, 23.3 ± 1.6 g) in 2000 kcal. The amount is far in excess of the recommended amount for the Japanese population, 17 g/day for women and 20 g/day for men (Table 1).

Each patient’s dietary pattern was assessed by means of a food-frequency questionnaire. When the following 2 conditions were fulfilled, it was regarded as SVD. One is that a patient follows the principle of SVD: daily intake of rice, vegetables, and fruits, and occasional intake of fish, meat, and other animal-based foods. The other is that a patient refrains from foods reported as risk factors for IBD in or outside Japan. A diet that did not fulfill these 2 conditions was regarded as an omnivorous diet. Compliance to SVD was 100% among inpatients and 73% among outpatients. There was no untoward effect of SVD in our study. The remission rate with
combined infliximab and SVD for newly diagnosed CD was 100% (unpublished observation). Maintenance of remission on SVD was 92% at 2 years (Figure 2). This was obtained without scheduled maintenance therapy with biologic drugs. Because these excellent short- and long-term results are not obtained by the current low-residue diet they can partly be explained by SVD.

CONCLUSION

Although the precise mechanism is to be determined, epidemiology provides convincing evidence that a plant-based diet is a healthy diet providing therapeutic and/or preventive effects against current major chronic diseases. Available data suggest the rationale to use dietary fiber in the treatment of IBD. We believe a plant-based diet not only is effective for gut inflammation but also promotes the general health of IBD patients. A plant-based diet inevitably contains considerable amounts of dietary fiber. A high amount of dietary fiber is not harmful and seems to be favorable for CD.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

Mary Corrado, ELS, provided editorial assistance.

References


Cure

Diet cures more than the lancet.
ORIGINAL RESEARCH & CONTRIBUTIONS

Special Report

A Plant-Based Diet, Atherogenesis, and Coronary Artery Disease Prevention

Phillip Tuso, MD, FACP, FASN; Scott R Stoll, MD; William W Li, MD

ABSTRACT

A plant-based diet is increasingly becoming recognized as a healthier alternative to a diet laden with meat. Atherosclerosis associated with high dietary intake of meat, fat, and carbohydrates remains the leading cause of mortality in the US. This condition results from progressive damage to the endothelial cells lining the vascular system, including the heart, leading to endothelial dysfunction. In addition to genetic factors associated with endothelial dysfunction, many dietary and other lifestyle factors, such as tobacco use, high meat and fat intake, and oxidative stress, are implicated in atherogenesis. Polyphenols derived from dietary plant intake have protective effects on vascular endothelial cells, possibly as antioxidants that prevent the oxidation of low-density lipoprotein. Recently, metabolites of L-carnitine, such as trimethylamine-N-oxide, that result from ingestion of red meat have been identified as a potential predictive marker of coronary artery disease (CAD). Metabolism of L-carnitine by the intestinal microbiome is associated with atherosclerosis in omnivores but not in vegetarians, supporting CAD benefits of a plant-based diet. Trimethylamine-N-oxide may cause atherosclerosis via macrophage activation. We suggest that a shift toward a plant-based diet may confer protective effects against atherosclerotic CAD by increasing endothelial protective factors in the circulation while reducing factors that are injurious to endothelial cells. The relative ratio of protective factors to injurious endothelial exposure may be a novel approach to assessing an objective dietary benefit from a plant-based diet. This review provides a mechanistic perspective of the evidence for protection by a plant-based diet against atherosclerotic CAD.

INTRODUCTION

Despite the remarkable work done by physicians to treat coronary artery disease (CAD), heart disease is still the leading cause of death in the US.1 A Western diet containing large amounts of sugar, salt, cholesterol, and fat can lead to diabetes mellitus, high blood pressure, hyperlipidemia, obesity, and CAD. Major CAD risk factors, such as tobacco use, hypercholesterolemia, hypertension, and diabetes, have all been found to cause vascular endothelial cell (VEC) injury and dysfunction.2 VEC injury and dysfunction lead to atherogenesis, atherosclerosis, and atherothrombotic CAD. Recent literature suggests that lifestyle management that includes a diet of mostly plants may help prevent and reverse CAD.3 Plant-based nutrition is the predominant consumption of plant-based, whole foods to obtain macronutrients (carbohydrates, protein, and fats), micronutrients (vitamins and minerals), and bioactive components (eg, flavonoids, plant sterols, polyphenols) that optimize body function. It is a conscious and mindful decision to maximize the health benefits per calorie while minimizing potential harmful exposures. A plant-based diet is by definition low in fat, cholesterol, salt, animal products, and sugar. As a result, a plant-based diet is associated with a lower incidence of CAD and thus lower costs associated with the treatment of CAD. Therefore, changing from a Western diet to a plant-based diet may be a simple, low-cost intervention that prevents atherothrombotic CAD.

The primary aim of the plant-based diet is to maximize the consumption of nutrient-dense plant foods while minimizing processed foods, added sugars, oils, and animal-based foods.4 A plant-based diet encourages lots of vegetables and fruits and is low in fat.5 Broadly defined, a plant-based diet has significant health benefits, and studies have shown that a plant-based diet can be an effective treatment for obesity,6-8 diabetes,9-14 hypertension,15 hyperlipidemia,16 and heart disease.17,18

The Lifestyle Heart Trial found that 82% of patients diagnosed with heart disease who followed this plant-based diet program had some level of regression of atherosclerosis and 91% had a reduction in the frequency of angina episodes, whereas 53% of the control group, fed the American Heart Association diet, had progression of atherosclerosis.19 In addition, the study showed a reduction in low-density lipoprotein (LDL) (37.2%) that is similar to results achieved with lipid-lowering medications. Similarly, other researchers showed that compared with a control group, the plant-based diet group had a 73% decrease in coronary events and a 70% decrease in all-cause mortality.20 In 1998, a collaborative analysis using original data from 5 prospective studies was reviewed and showed that, compared with nonvegetarians, vegetarians had a 24% reduction in ischemic heart disease death rates.19

Atherothrombotic CAD is a largely preventable condition that is characterized by the formation of atherosclerotic plaques. Atherosclerotic lesions are the result of an excessive,
VECs are ac
Macrophages release cytokines that recruit more monocytes to subendothelial space
Monocytes adhere to VEC
Foam cells release cytokines that cause smooth muscle formation resulting in formation of fibrous cap
Monocytes differentiate into macrophages
VECs are dysfunctional after they are injured, resulting in an inflammatory response. Dysfunctional VECs lose the ability to produce nitric oxide and to prevent adhesion of platelets, LDL, and monocytes to the VEC. As a result, LDL and monocytes adhere and migrate into the subendothelial space. In the subendothelial space, LDL becomes oxidized and promotes monocyte transformation to macrophages. In addition, more macrophages are recruited to the area of abnormal endothelium by the expression of cell adhesion molecules and cytokines and are activated by oxidized LDL (OxLDL). Macrophages absorb the OxLDL, leading to further activation and enlargement and creating foam cells and fibrous plaques. Activated macrophages secrete effector molecules that kill cells, degrade the extracellular matrix, and increase vascular smooth muscle cell apoptosis, promoting plaque formation and destabilization. Over time and with repeated VEC injury, arteries narrow and become diseased with the penultimate rupture of unstable plaques in coronary arteries, leading to complete occlusion of the artery, ischemia, and death.

CORONARY ARTERY DISEASE PREVENTION

Vascular Endothelial Cell Injury

VECs play a key role in the regulation of vascular homeostasis, and increasing evidence suggests that alterations in endothelial function contribute to the pathogenesis and clinical expression of CAD. Causes of initial VEC injury include elevated LDL levels, elevated blood sugar levels, diabetes, and high blood pressure. Recent studies show that lifestyle management with diet may prevent diabetes, lower blood pressure levels, lower LDL levels, and prevent CAD events and death. Therefore, changing to a plant-based diet may decrease CAD mortality by interrupting or reversing the process of atherogenesis. A plant-based diet decreases the intake of substances found in processed foods, added sugars, oils, and meats that promote atherosclerosis with a reciprocal increased intake of bioactive substances found in plants that protect the endothelium and inhibit atherogenesis.

Low-Density Lipoprotein Oxidation

Epidemiologic data have shown that people with a high consumption of fruit and vegetables are at a lower risk of death compared with those with a low consumption. Data from the Nurses’ Health Study demonstrated an inverse relationship between fruit and vegetable intake and CAD, and each additional serving of leafy green vegetables per day resulted in a 11% decreased risk for CAD. Other epidemiologic
studies suggest that higher polyphenol intake from a plant-based diet is associated with decreased risk for CAD.\textsuperscript{35-37} Studies have also shown that decreased intake of flavonoids may be associated with an increased risk of myocardial infarction.\textsuperscript{38} A systematic review by Mente et al\textsuperscript{39} in 2009 suggested there is strong evidence that a plant-based diet may protect against CAD whereas a Western diet may promote CAD. One mechanism by which a plant-based diet may promote health is via the positive effects of polyphenols. A review by Vita\textsuperscript{25} suggests that the reduced risk of CAD events may be related to the beneficial effect polyphenols have on endothelial cell function. On the basis of cell culture studies, polyphenols may positively affect critical steps in atherogenesis, including LDL oxidation, nitric oxide release, inflammation, oxidative stress, cell adhesion, foam cell formation, smooth muscle cell proliferation, and platelet aggregation.\textsuperscript{40} Evidence suggests that individuals with the highest polyphenols intake have modestly reduced risks for CAD.\textsuperscript{36,41-46} There is increasing evidence that flavonoids may have beneficial effects on VEC control of thrombosis, inflammation, and vascular tone.\textsuperscript{25} Polyphenols may also have beneficial effects limiting platelet adhesion and aggregation that can precipitate acute coronary syndromes after plaque rupture. Diet may also influence the effects of risk factors on VEC function. Prospective studies have shown that endothelial dysfunction is associated with an increased risk of CAD events.\textsuperscript{47-49} Many interventions known to reduce CAD risk have the ability to reverse endothelial dysfunction.\textsuperscript{50} These findings suggest that endothelial function may have utility as a surrogate marker of CAD risk. Furthermore, endothelial function has evolved into a clinically useful endpoint for studies of potential interventions for the prevention or treatment of CAD.

Nitric oxide released from VEC via the endothelial nitric oxide synthase is a vasoprotective molecule.\textsuperscript{51} In addition to promoting vasodilatation, VEC nitric oxide has antiatherosclerotic properties that include inhibition of platelet aggregation, of leukocyte adhesion, and of smooth muscle cell proliferation.\textsuperscript{51} Therefore, VEC nitric oxide production via endothelial nitric oxide synthase is a significant target to prevent and to treat CAD. Leikert et al\textsuperscript{52} showed that an alcohol-free red wine polyphenol extract strongly increases nitric oxide release, endothelial nitric oxide synthase, and endothelial nitric oxide synthase expression after long-term incubation of human endothelial cells.

To explore this possibility, researchers investigated the effects of tea consumption on endothelial function. Tea contains an assortment of water-soluble antioxidant flavonoids that

![Figure 2: Proinflammatory gene expression and lifestyle modification.\textsuperscript{1}](image)

Figure 2 shows proinflammatory gene expression of 8 genes (see below) from individuals who completed a year-long lifestyle modification program that consisted of a low-fat vegetarian diet, 180 minutes of physical activity per week, and stress reduction classes. Compared with a matched control group, the participant group showed a validated differential reduction in gene expression of proinflammatory genes involved in neutrophil activation and molecular pathways important to vascular function.

Gene Symbol = Gene Name (Gene Ontology Biologic Process)

\begin{tabular}{|c|c|}
\hline
LTF & lactotransferrin (immune response) \\
LCN2 & lipocalin (transporter activity) \\
CEACAM8 & carcinoembryonic antigen-related (immune response) \\
CRISP3 & cysteine-rich secretory protein 3 (immune response; defense response) \\
HP & haptoglobin protein (defense response) \\
OLFM4 & olfactomedin4 (cell adhesion) \\
CAMP & cathelicidin antimicrobial peptide (defense response) \\
BPI & bactericidal/permeability-increasing protein (immune response; lipid binding) \\
\hline
\end{tabular}

have been shown to have a beneficial effect on endothelial function and possibly nitric oxide production. Other flavonoid-containing beverages, such as grape products, have been shown to improve endothelial function and LDL oxidation in adults with angiographically proven CAD.

Zamora-Ros and colleagues evaluated the relationship between total urinary polyphenols and all-cause mortality during a 12-year period among older adult participants. The study population included 807 men and women aged 65 years and older from Tuscany, Italy. During the 12-year follow-up, 274 participants died. At enrollment, total urinary polyphenols excretion tended to be greater in participants who survived than in those who died. In the multivariable Cox model, participants in the highest tertile of total urinary polyphenols at enrollment had a mortality rate lower than those in the lowest tertile. The authors concluded that total urinary polyphenols is an independent risk factor for mortality among community-dwelling older adults and that a high dietary intake of polyphenols may be associated with longevity. Studies have shown that polyphenols may have an effect on LDL oxidation. In one study, dietary polyphenols reduced plasma LDL oxidation by 20%. In another study, resveratrol and alcohol-free wine polyphenols protected LDL from oxidation. These data suggest that polyphenols found in fresh fruits and vegetables may help prevent atherogenic lesions by down-regulating oxidation of LDL.

**Macrophage Activation**

Consuming large amounts of red meat is a risk factor for heart disease. Researchers prospectively followed 84,136 women aged 30 to 55 years in the Nurses’ Health Study during a 26-year period. The authors reported that higher intakes of red meat were significantly associated with elevated risk of heart disease. A subsequent study reached a similar conclusion in a cohort of male physicians. Men in the highest quintile for red meat consumption had a 24% increase in risk of heart failure compared with men in the lowest quintile of consumption.

This strong association between heart disease and consumption of red meat is further supported by recent studies. Studies in animals and humans showed a mechanistic link between intestinal microbial metabolism of nutrients in red meat (choline and L-carnitine) and CAD through the production of a pro-atherosclerotic metabolite called trimethylamine-N-oxide (TMAO). Another article published in *Nature Medicine* reported that omnivorous human subjects were found to produce more TMAO than did individuals who consumed primarily a plant-based diet (vegans or vegetarians). A recent study in the *New England Journal of Medicine* reported that TMAO levels are predictors of CAD. The researchers followed 4007 patients, primarily men, undergoing elective angiography for evaluation of possible coronary disease; none had experienced acute coronary syndromes for 3 years. Elevated TMAO levels were associated with an increased risk of major cardiovascular events (hazard ratio for highest vs lowest TMAO quartile, 2.54; 95% confidence interval, 1.96 to 3.28; p < 0.001). Wang et al reported that TMAO produced from red meat nutrients may play a role in promoting atherosclerosis by possibly activating macrophages and foam cells.

To further study the effect that diet may have on risk factors for atherosclerosis and macrophage activation, Ellsworth et al looked at CAD risk factor reduction and peripheral blood gene expression in patients who participated in a year-long lifestyle management program compared with a control group that did not participate. The one-year lifestyle management program included a plant-based diet, 180 minutes per week of moderate aerobic exercise, and a stress-management program. Among participants in the lifestyle-change program, at one year, the prevalence of hypertension decreased from 41% to 17%, obesity rates decreased from 60% to 37%, and the rate of dyslipidemia decreased from 54% to 37%. The researchers also found that lifestyle modification effectively reduced expression of pro-inflammatory genes associated with neutrophil (macrophage) activation and the pathogenesis of atherosclerosis (Figure 2). Gene expression was not modified by medications in the matched control group.

**DISCUSSION**

Plant-based nutrition can prevent diabetes, high blood pressure, and CAD events. The benefits of a predominantly plant-based nutritional regimen deserve further consideration on the basis of the information presented in this article. Compared with people who frequently consume red meat, people who eat less red meat and consume more vegetables have lower body mass index, lower systolic blood pressure, lower serum levels of LDL, and thinner blood vessel intimal medial wall thickness. Finally, consumption of a heavily plant-based diet has been shown to result in less oxidative stress and less micro-inflammation compared with omnivores’ meat-centric diet.

Reducing risk factors for atherosclerosis with a plant-based diet may help us to understand the potential a plant-based diet has on down-regulating the process of atherogenesis and atherothrombotic CAD. Therefore, food may be medicine and the power of lifestyle management in disease prevention should not be ignored. Compared with drug therapy, angiography/stent placement, and bypass surgery, a plant-based diet may be a low-cost intervention that can prevent and reverse atherosclerotic CAD.

Ninety-three percent of Americans are omnivores and are unlikely to give up meat. Historically, humans have consumed meat in varying amounts based upon environmental accessibility to plant-based foods and general food scarcity. Industrialization has allowed meat to become a central part of our food culture and our plates, and it is highly regarded as the best source of protein. The data presented in this article suggest that once we develop a plant-based diet microbiota, our bacteria will not convert phosphatidylcholine or L-carnitine to TMAO with the occasional consumption of meat. In addition, the data presented in this article suggest that polyphenols from fresh fruits and vegetables increased survival and that elevated TMAO levels from red meat were associated with decreased survival. In light of this new information, we may consider measuring the ratio of polyphenols to TMAO as an indicator of atherogenesis risk. Reducing...
the risk factors for atherogenesis will significantly reduce the downstream risk of atherosclerosis, atherothrombotic CAD, and myocardial infarction.

Finally, as more data become available in the literature, we may want to consider how healthy eating can systematically prevent atherosclerosis. In this article, we present a proposed mechanism for how a plant-based diet may prevent atherosclerosis and CAD events (Figure 1). This includes 1) prevention of VEC injury by eating foods low in sugar, salt, and fat; 2) prevention of LDL oxidation by increased intake of fresh fruits and vegetables containing antioxidants, such as polyphenols; and 3) prevention of macrophage activation by decreasing intake of red meat, by exercise, and by stress reduction.

CONCLUSION
VEC injury may occur in individuals who do not have clini-
cally active CAD but who have risk factors for CAD, such as smoking, hypercholesterolemia, diabetes, and hypertension.41 Because abnormal endothelial function is an early marker of CAD, the endothelium appears to be an ideal target for preventive therapy. Because we do not have specific markers for endothelial cell dysfunction, evidence presented in this article suggests that levels of urinary polyphenols (as a marker of fruit and vegetable consumption), blood TMAO levels (as a marker for red meat consumption), and proinflammatory gene expression of genes involved in atherogenesis may indicate the VEC milieu that promotes VEC health versus VEC injury. Elevating levels of blood polyphenols and lowering blood TMAO levels by eating a plant-based diet may promote health of VECs and prevent atherosclerotic CADs by at least three different proposed mechanisms. More research in this area is needed so in the future we may have objective measures of healthy eating that will promote VEC wellness years before the development of atherosclerosis and CAD.

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Acknowledgment
Mary Corrado, ELS, provided editorial assistance.

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11. Campbell TC, Campbell TM II. The China Study: the most comprehensive study of nutrition ever conducted and the starting implications for diet, weight loss, and long-term health. Dallas, TX: Ben Bella Books; 2006 May 11.

The author(s) have no conflicts of interest to disclose.


Acupuncture Safety in Patients Receiving Anticoagulants: A Systematic Review

Michael McCulloch, LAc, MPH, PhD; Arian Nachat, MD; Jonathan Schwartz; Vicki Casella-Gordon, RN, MS, CNS; Joseph Cook, JD

ABSTRACT
Introduction: Theoretically, acupuncture in anticoagulated patients could increase bleeding risk. However, precise estimates of bleeding complication rates from acupuncture in anticoagulated patients have not been systematically examined.

Objective: To critically evaluate evidence for safety of acupuncture in anticoagulated patients.

Methods: We searched PubMed, EMBASE, the Physiotherapy Evidence Database, and Google Scholar.

Results: Of 39 potentially relevant citations, 11 met inclusion criteria: 2 randomized trials, 4 case series, and 5 case reports. Seven provided reporting quality sufficient to assess acupuncture safety in 384 anticoagulated patients (3974 treatments). Minor-moderate bleeding related to acupuncture in an anticoagulated patient occurred in one case: a large hip hematoma, managed with vitamin K reversal and warfarin discontinuation following reevaluation of its medical justification. Blood-spot bleeding, typical for any needling/injection and controlled with pressure/cotton, occurred in 51 (14.6%) of 350 treatments among a case series of 229 patients. Bleeding deemed unrelated to acupuncture during anticoagulation, and more likely resulting from inappropriately deep needling damaging tissue or from complex anticoagulation regimens, occurred in 5 patients. No bleeding was reported in 2 studies (74 anticoagulated patients): 1 case report and 1 randomized trial prospectively monitoring acupuncture-associated bleeding as an explicit end point. Altogether, 1 moderate bleeding event occurred in 3974 treatments (0.003%).

Conclusion: Acupuncture appears to be safe in anticoagulated patients, assuming appropriate needling location and depth. The observed 0.003% complication rate is lower than the previously reported 12.3% following hip/knee replacement in a randomized trial of 27,360 anticoagulated patients, and 6% following acupuncture in a prospective study of 229,230 all-type patients. Prospective trials would help confirm our findings.

INTRODUCTION
Acupuncture is a healing method intended to regulate physiologic and neurologic functioning, with the earliest archeologic evidence for acupuncture tools dating to Neolithic times, and the earliest textual evidence of acupuncture written in the Shang Dynasty (1766 BC to c1046 BC). Acupuncture needle stimulation achieves its therapeutic benefits through up-regulation of processes in the cortical network and down-regulation in the limbic-paralimbic neocortical network. Its effect on pain is a combination of simultaneous changes in sensory, cognitive, and affective pathways. Acupuncture is efficacious in patients with conditions for whom anticoagulant medications are often prescribed; those with cancer, atrial fibrillation, acute ischemic stroke, postischemic stroke, postoperative pain, renal disease, and critically ill intensive care patients or those receiving mechanical ventilation. Acupuncture needles used in practice range from 0.12 mm (Japanese gauge 28) to 0.35 mm (Chinese gauge 28); however, in our data searches we identified no reports examining any effect of needle gauge on acupuncture treatment safety.

Anticoagulants are widely used in the hospital and community care settings to prevent coagulopathies and embolic phenomena, with demonstrated safety. Meta-analysis of randomized trials comparing anticoagulant prophylaxis with no treatment in 19,958 hospitalized (not perioperative) patients showed a nonsignificant increase in major bleeding. Older but commonly used anticoagulants include clopidogrel for recent stroke or cardiac stents; warfarin for prevention of thromboembolism in patients with atrial fibrillation or with history of deep-vein thrombosis or pulmonary embolism; and low-molecular-weight heparin, unfractionated heparin, or vitamin K antagonists for prevention of thromboembolism in long-term inpatients and those with cirrhosis or cancer. Newer drugs include the Factor X inhibitors (fondaparinux, rivaroxaban, and apixaban) for atrial fibrillation and prevention of surgery-associated coagulopathy and direct thrombin inhibitors (hirudin and its derivatives, argatroban, elagatran, abigatran) for atrial fibrillation and venous thromboembolism.

To place our review in a broader context of patients receiving low-molecular weight heparin, unfractionated heparin, or vitamin K antagonists, we conducted a meta-analysis of randomized trials comparing anticoagulant prophylaxis with no treatment in 19,958 hospitalized (not perioperative) patients. We observed a nonsignificant increase in major bleeding.

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weight heparin or vitamin K antagonists, the safety of surgical procedures far more invasive than acupuncture has been closely examined. A Cochrane meta-analysis of 27,360 anticoagulated patients found 123 bleeding events per 1000 patients (12.3%) occurring in the 4 to 6 weeks following total hip or knee replacement.26

The risk of procedure-related bleeding in anticoagulated patients receiving acupuncture may be lower, but the question has not yet been definitively investigated. We therefore conducted this meta-analysis to review all identifiable peer-reviewed medical publications and critically examine the safety of acupuncture in patients receiving anticoagulant therapy.

**MATERIALS AND METHODS**

We searched PubMed, EMBASE, the Physiotherapy Evidence Database, and Google Scholar to identify potentially relevant citations. Search terms for our PubMed and EMBASE searches are listed in the Sidebars: PubMed Search Terms and EMBASE Search Terms.

We searched other databases with comparable terms. Two reviewers screened all citations and conferred with a third when disagreements arose in deciding on inclusion or exclusion of citations. Exclusion criteria were as follows: no discussion of both anticoagulants AND acupuncture, no quantifiable data, anticoagulant use not confirmed, and adverse events not reported.

We ordered 39 articles that were potentially relevant and, upon review of the full-text copies and exclusions (Figure 1), identified 11 that met inclusion criteria: reporting on the combination of acupuncture and 1 or more anticoagulants. After data extraction, we conferred to assess these 11 articles and, combining clinical judgment with literature assessment criteria, graded them by quality of reporting and apparent likelihood of a causal relationship between anticoagulant exposure and acupuncture-associated bleeding. To facilitate clear risk stratification, these articles were grouped into likelihood of certainty that the outcome (bleeding event) was attributable to the co-exposure (acupuncture, in patients receiving anticoagulants). We assessed that likelihood of certainty on the basis of the elapsed time between anticoagulant dosing and acupuncture as well as on the quality and thoroughness of documentation of each therapy in the published manuscripts. Data from the full-text articles were then extracted into table format (Table 1).27-36

**RESULTS**

**Systematic Search**

Our systematic search yielded 11 relevant citations (Figure 1): 2 randomized trials,29,33 3 retrospective case series,28,34,36 5 case reports,27,31,32,37,38 and 1 practice description.35 Because we did not find multiple studies with control patients or before-after comparisons, quantitative meta-analysis was not performed, and we report the results as a systematic review (Table 1).

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### Table 1: Potentially relevant citations identified and screened for retrieval (N = 39)

<table>
<thead>
<tr>
<th>Source</th>
<th>N</th>
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</thead>
<tbody>
<tr>
<td>PubMed</td>
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<tr>
<td>EMBASE</td>
<td>2</td>
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<tr>
<td>Google Scholar</td>
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Figure 1. QUOROM Statement flow diagram. Safety of acupuncture in patients receiving anticoagulants: a systematic review.

PEDro = Physiotherapy Evidence Database.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Sample size</th>
<th>Study type</th>
<th>Patients</th>
<th>Anticoagulants specified</th>
<th>Acupuncture method</th>
<th>Complication</th>
<th>Complication management</th>
<th>Time between anticoagulant and acupuncture</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenz, 2012</td>
<td>N = 1</td>
<td>Case report</td>
<td>82-year-old woman</td>
<td>Warfarin</td>
<td>Not specified</td>
<td>Hematoma, right buttock/upper thigh</td>
<td>Warfarin stopped, oral vitamin K given</td>
<td>Concurrent</td>
<td>Attribution of bleeding to acupuncture is reasonable</td>
</tr>
<tr>
<td>Miller, 2012</td>
<td>N = 229 (350 tx)</td>
<td>Retrospective case series</td>
<td>106 men 123 women age 29-95 years</td>
<td>Warfarin</td>
<td>Not specified</td>
<td>Drop of blood after needle withdrawal in 14.6% (n = 51)</td>
<td>Pressure with cotton-tipped swab (for n = 50); not specified for the remaining patient</td>
<td>Concurrent</td>
<td>Cases directly observed. No difference in bleeding between high INR vs low (14.3% vs 14.6%)</td>
</tr>
<tr>
<td>Li, 2003</td>
<td>N = 80</td>
<td>RCT</td>
<td>Age 42-74 years, gender unspecified</td>
<td>Dextran/aspin in all, randomized to: scalp acupuncture urokinase saline placebo</td>
<td>Scalp, and GB20</td>
<td>Intracranial hemorrhage: 1 case in dextran/ aspin + scalp acupuncture group, 2 cases in dextran/ aspin + urokinase group, and 1 case in dextran/ aspin + saline placebo</td>
<td>Not specified</td>
<td>Concurrent</td>
<td>Reported 3% complication rate is less than the rate reported by AHA/ASA as typical in acute ischemic stroke patients receiving multi-agent fibrinolytics without acupuncture</td>
</tr>
<tr>
<td>Nishimura, 2008</td>
<td>N = 1</td>
<td>Case report</td>
<td>81-year-old woman</td>
<td>Limprostat alfadex</td>
<td>Not specified</td>
<td>Bleeding from rupture of extensor tendons by acupuncture needle</td>
<td>Decompression surgery</td>
<td>Concurrent</td>
<td>Likely caused by inappropriately deep needling regardless of anticoagulant therapy</td>
</tr>
<tr>
<td>Lee, 2005</td>
<td>N = 1</td>
<td>Case report</td>
<td>75-year-old woman</td>
<td>Warfarin and aspirin</td>
<td>Not specified</td>
<td>Cecal intradural hematoma</td>
<td>Right hemicolecotomy</td>
<td>Concurrent</td>
<td>Very likely the result of inappropriately deep needling</td>
</tr>
<tr>
<td>Xu, 2005</td>
<td>N = 70</td>
<td>RCT</td>
<td>Age 39-78 years (mean 61.4 years)</td>
<td>LMW heparin, urokinase</td>
<td>CV17, P6, Sp6, P4</td>
<td>No serious AEs, however minor AEs not reported</td>
<td>Not specified</td>
<td>Concurrent</td>
<td>Minor adverse events not reported</td>
</tr>
<tr>
<td>Sciammarella, 2002</td>
<td>N = 4 (51 tx)</td>
<td>Case series</td>
<td>4 women age 56-64 years</td>
<td>Warfarin</td>
<td>Not specified</td>
<td>Bruise size typical for acupuncture, 1 person</td>
<td>Not specified</td>
<td>Concurrent</td>
<td>No patients had posttreatment external bleeding</td>
</tr>
</tbody>
</table>

**Table 1. Published data on acupuncture complications in patients receiving anticoagulant medication therapy**

**Quality of reporting sufficient to allow assessment of acupuncture safety in anticoagulated patients**

**Minor-moderate bleeding related to acupuncture in an anticoagulated patient**

**Minors blood-spot bleeding typical for any needling procedure and not normally considered a problem in medical practice**

**Bleeding unlikely related to acupuncture and more likely the result of multi-agent fibrinolytics**

**Bleeding caused by inappropriately deep needling, certain to have occurred even in patients not receiving anticoagulants**

**No bleeding observed**

**Quality of reporting insufficient to allow assessment of acupuncture safety in anticoagulated patients or to draw conclusions**

AEs = adverse events; AHA/ASA = American Heart Association/American Stroke Association; INR = international normalized ratio; LMW = low-molecular-weight; RCT = randomized controlled trial; tx = treatments.
Articles with Quality of Reporting Allowing Assessment of Safety of Acupuncture in Anticoagulated Patients

We sought clear documentation of time between anticoagulation and acupuncture therapy as well as an adequate description of adverse events observed. We found seven publications with quality of reporting sufficient to assess whether the safety of acupuncture was influenced by concurrent anticoagulant therapy (Table 1).27-29,31-34

Minor bleeding typical to that seen in both acupuncture and medication injection (a drop of blood managed simply with pressure and cotton-tipped swab) was observed in 35 (14.6%) of 230 patients by a physician acupuncturist at a solo-practice physician’s office to receive acupuncture for pain relief, all 4 patients were receiving warfarin for underlying conditions. Cumulatively, the 4 women received 51 acupuncture treatments without electrical stimulation at local and distal acupuncture points. After treatment, none of the patients demonstrated any bleeding or bleeding-related problems, except for an occasional asymptomatic bruise at an acupuncture site on the upper back on one patient.34

Significant bleeding (most likely related to aggressive anticoagulation and not to acupuncture) was reported in a randomized trial comparing two different acupuncture methods in the treatment of 80 patients with acute ischemic cerebral infarction up to 6 hours after attack, in which intracranial hemorrhage was a reported outcome. Patients were randomized to 3 groups: A) dextran/aspirin + scalp acupuncture, B) dextran/aspirin + urokinase, and C) dextran/aspirin + saline placebo. The authors reported 4 cases of intracranial hemorrhage: 1 case in the dextran/aspirin + scalp acupuncture group, 2 cases in the dextran/aspirin + urokinase group, and 1 case in the dextran/aspirin + saline placebo group.29,30

Significant bleeding apparently caused by inappropriately deep needling (likely to have happened even if the patient had not been anticoagulated) was observed in 2 case reports: acute carpal tunnel syndrome including bleeding from rupture of several extensor tendons of the hand the day after acupuncture in an 81-year-old woman receiving (unspecified) anticoagulant therapy, managed surgically31; and multiple small hematomas on the inner membrane of the appendix in a 75-year-old woman following acupuncture with long needles placed at a depth that repeatedly pierced the intestine wall.32

The remaining 2 high-quality reports documented no acupuncture-induced bleeding. In a trial of 70 patients randomized to either aspirin/low-molecular-weight heparin anticoagulation, or anticoagulation combined with acupuncture, there were no serious adverse events reported, although the article did not include reporting of minor adverse events.33 In a retrospective chart review of the outcomes of 4 women who presented to a solo-practice physician’s office to receive acupuncture for pain relief, all 4 patients were receiving warfarin for underlying conditions. Cumulatively, the 4 women received 51 acupuncture treatments without electrical stimulation at local and distal acupuncture points. After treatment, none of the patients demonstrated any bleeding or bleeding-related problems, except for an occasional asymptomatic bruise at an acupuncture site on the upper back on one patient.34

Articles with Quality of Reporting Insufficient to Assess Safety of Acupuncture in Anticoagulated Patients or to Draw Conclusions

In a practice review conducted at the Dana Farber Cancer Institute (Boston, MA), the authors reported that in their experience in treatment of more than 6000 oncology patients, acupuncture did not increase the chance of bleeding (rates not specified) in oncology patients receiving anticoagulants.35 In a retrospective case series of several hundred patients by a physician acupuncturist at a Toronto spinal cord injury rehabilitation hospital, the author reported her personal experience during an 11-year period, observing not a single incident of bleeding from acupuncture in anticoagulated patients; however, this was a letter to the journal editor and may have been written more from memory than formal retrospective case review.36 In addition, 2 case reports noted hematoma38 and compartmental hemorrhage37 caused by giving warfarin to acupuncture patients, but the time between acupuncture and anticoagulation was not specified. Because of the poor quality of reporting in these 4 articles, we were unable to draw conclusions and withdrew them from the review set.

DISCUSSION

We determined that 7 of the 11 articles identified in our systematic search provided reporting of sufficient quality to critically assess our research question: does acupuncture in anticoagulated patients present a higher-than-expected risk of bleeding? Of the anticoagulated patients treated with acupuncture discussed in the 7 articles, there were 58 bleeding events documented in 3974 treatments among 384 acupuncture patients, a bleeding complication rate of 1.4%. This compares very favorably with the 12.3% bleeding complication rate in patients anticoagulated with low-molecular-weight heparin or vitamin K antagonists who receive total hip or knee replacement. Remarkably, the 1.4% acupuncture bleeding complication rate is lower than the 6% rate documented in a large prospective observational study of 229,230 patients, a diverse group without restrictive exclusion criteria.39

The majority of acupuncture bleeding events found in our study were either an asymptomatic bruise40 or a minor drop of blood typical of any needling procedure and managed with pressure and cotton.28 However, the bleeding was not clinically significant and stopped with pressure. By our assessment, the only serious bleeding events were the result of either inappropriately deep needling (for two patients)41,42 or mixtures of anticoagulation regimens.29 In the randomized trial by Li et al.43 each group observed intracranial hemorrhage: dextran/aspirin + scalp acupuncture (one case), dextran/aspirin + urokinase (two cases), and dextran/aspirin + saline placebo (one case). These observations do not support assigning causation of hemorrhage to the combination of acupuncture and anticoagulants but rather...
suggest anticoagulant combinations were a larger problem. The remaining 2 high-quality reports documented no acupuncture-induced bleeding. In a trial of 70 patients randomized either to aspirin/low-molecular-weight heparin anticoagulation alone or to anticoagulation combined with acupuncture, the authors reported that there were no serious adverse events (however, they did not include data on minor adverse events). The second was a retrospective chart review of the outcomes of 4 women given acupuncture for pain relief (totaling 51 acupuncture treatments), with only an occasional asymptomatic bruised area at an acupuncture site on the upper back on 1 patient. For the 4 remaining cases that we identified, the relationship between the bleeding event and the combination of acupuncture and anticoagulants was indeterminable. Two case reports documented calf compartment syndrome following acupuncture treatments, but we determined causation was not assessable because the duration between acupuncture and anticoagulation was not specified. Unfortunately the final publication, a 6000-patient retrospective practice review, which could have been well positioned to comprehensively address the question of the safety of acupuncture in patients receiving anticoagulants, was lacking in reporting depth and assessment of causation was not possible.

CONCLUSION

Given that 56 of 384 patients (39.74% treatments; 1.4%) experienced minor bleeding and only 1 patient (0.02%) experienced serious bleeding likely related to the combination of anticoagulant therapy and acupuncture, the evidence identified and assessed in our systematic review suggests acupuncture has a high degree of safety in patients receiving anticoagulant therapy. The fact that the only significant bleeding occurred in patients whose acupuncturist caused tendon and organ damage underscores the importance of respecting appropriate needleling location and depth. A prospective randomized trial similar to the one randomized trial53 we identified but that monitored for both minor and major bleeding events following acupuncture in anticoagulated patients, would help to confirm the findings of our systematic review.

Our systematic review noted a large difference between our observed complication rate and that of Witt et al. To further clarify the differences between that article and our own favorable safety observations within our institution, we plan on following up this review with retrospective and then prospective analyses of original patient data on the safety of acupuncture in anticoagulated patients.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgment

Mary Corrado, ELS, provided editorial assistance.

References


Acupuncture Safety in Patients Receiving Anticoagulants: A Systematic Review


A Beautiful Theoretical System

There is hardly a field in all of historical scholarship of which we know so little as the development of Chinese medical thought. A mountain of books which treat this subject has accumulated in the West since the sixteenth century. Some are written by European practitioners, since acupuncture is now a flourishing enterprise in the Occident, and some by scholars. But most of these writings, regardless of origin, obscure rather than illuminate the beautiful Chinese theoretical system.

— Nathan Sivin, b 1931, American author, scholar, sinologist, historian, essayist, professor emeritus of Chinese Culture and the History of Science
CASE STUDY

An Idiosyncratic Reaction to Clopidogrel

Aaysha Kapila, MD; Lovely Chhabra, MD; Allison Diane Locke, MD; Pranav Patel, MD; Atul Khanna, MD; Chakradhar M Reddy, MD; Mark F Young, MD

ABSTRACT

Clopidogrel is an irreversible antiplatelet agent belonging to the thienopyridine group that acts to antagonize the adenosine diphosphate P2Y12 receptor on platelets. It thus inhibits the activation of platelet glycoprotein GPIIb/IIIa complex, which is essential for fibrinogen—platelet complex formation. Clopidogrel has widely replaced ticlopidine because of a much better clinical safety profile. Clopidogrel is a prodrug that requires hepatic activation to exert its antiplatelet effect. Hepatotoxicity with use of clopidogrel is rare but clinically significant phenomenon. We report a case of clopidogrel-induced hepatotoxicity in an elderly white woman.

INTRODUCTION

Clopidogrel is widely used in acute coronary syndrome interventions, for prevention of cerebral thromboembolism, and in neurointerventions such as coil placement in an unruptured aneurysm clipping. Clopidogrel is associated with a wide spectrum of adverse effects, including rash, indigestion, vomiting, diarrhea, thrombotic thrombocytopenic purpura, neutropenia, and aplastic anemia. Hepatotoxicity is an extremely rare and probably underrecognized side effect of clopidogrel. Despite the side effect profile, there are no standard guidelines for follow-up laboratory tests after initiation of clopidogrel. We herewith present the case of a 75-year-old white woman who presented to the hospital with nausea, vomiting, and fever lasting one day. A day before the current presentation, she had undergone an elective anterior cerebral communicating artery aneurysm clipping. Admission laboratory data were consistent with elevated liver enzymes for a mixed hepatotoxic and cholestatic pattern, along with anemia and thrombocytopenia. She had normal laboratory values 5 days before the current admission. Her only new medication, clopidogrel, had been started 5 days before the elective surgery. Viral hepatitis panel and acetaminophen levels were unremarkable. Results of Doppler ultrasound of the right upper quadrant and hepatobiliary iminodiacetic acid (HIDA) scan were normal. Clopidogrel was discontinued and intravenous antibiotics were initiated. The patient’s symptoms improved, and bilirubin and transaminases decreased. A postdischarge clinic follow-up revealed complete normalization of hemogram and liver enzymes. Clopidogrel was suspected to be the cause of hepatotoxicity in our patient, as suggested by the temporal correlation of drug therapy. All other etiologies for the liver disease were excluded, and the patient’s clinical response to drug withdrawal and rechallenge with medicine confirmed the diagnosis.

CASE STUDY

A 75-year-old white woman underwent an elective cerebral anterior communicating artery aneurysm clipping as empiric intervention to prevent a thrombotic cerebrovascular event. A day after the procedure, the patient presented to the emergency room with an acute febrile illness with symptoms of nausea, vomiting, bloating, and a fever of 38.2°C (100.8°F). She reported that she had been at her baseline health the previous night. She denied any alcohol or acetaminophen usage or any exposure to sick contacts. The patient’s only new medication, clopidogrel, had been started 5 days before the elective surgery. She denied any history of gallbladder problems or history of pancreatitis. The patient’s medical history was significant for hypertension, dyslipidemia, degenerative disc disease, and fibromyalgia. Social history was negative for alcohol, smoking, and illicit drug usage. Family history was significant for aneurysms and diabetes. She was allergic to penicillin, which caused anaphylaxis, aspirin, and azithromycin, which caused a rash. Her home medications included atorvastatin, levothyroxine, pregabalin, and risedronate. She had been on these medications for the previous 20 years without any adverse effects.

Her initial vital signs were unremarkable. A comprehensive systemic examination was only remarkable for a mild, diffuse abdominal tenderness without guarding or rigidity. Murphy sign was negative. Initial blood work, including complete blood count, was significant for a drop in hemoglobin to 11.4 mg/dL (previous value, 13.4 g/dL; normal, 12.4–15.2 g/dL). Hematocrit dropped to 34.9% (normal, 36.0–46.0%), and platelet count dropped to 114 K/μL (normal, 150–450 K/μL). The differential count for neutrophils was 88% (normal, 45%–75%). Comprehensive metabolic

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It is also ad
Day 7
It is
Day 14
Day 5
The patient was initially started on
Day 0
hospital Day 1 (5 days after initiation of clopidogrel),
and Day 14 (on follow-up in primary care physician’s office)

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 14</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
<td>48</td>
<td>1362</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>32</td>
<td>716</td>
</tr>
</tbody>
</table>

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

The patient was followed up in the
primary care office after 2 weeks, and
follow-up laboratory tests revealed complete normalization of the liver enzymes
(Table 1). After an informed discussion
with the patient, she was subjected to a
drug rechallenge on days 0, 2, and 7.

<table>
<thead>
<tr>
<th>Day 0</th>
<th>Day 2</th>
<th>Day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST (IU/L)</td>
<td>49</td>
<td>120</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>42</td>
<td>92</td>
</tr>
</tbody>
</table>

AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 1. Aspartate aminotransferase/alanine aminotransferase trend, preeadmission (Day 0), hospital Day 1 (5 days after initiation of clopidogrel), and Day 14 (on follow-up in primary care physician’s office)

Table 2. Aspartate aminotransferase/alanine aminotransferase trend after drug rechallenge on days 0, 2, and 7

The Maria and Victorino diagnostic
scale of hepatotoxicity score was 13,
indicating possible drug-induced liver injury. The score for temporal relationship
between the drug intake and the onset of the clinical picture was 3 points
because the onset of first clinical or
laboratory manifestations was less than
8 weeks (5 days). The score for exclusion
of alternative causes was 3 points
because viral hepatitis, alchololic liver
disease, and biliary tree obstruction
were ruled out. The score for extrabehatic manifestation was 2 points, with
our patient having fever and anemia on
presentation. The score for intentional
or accidental re-exposure to the drug was
3 points because the patient recovered
on drug rechallenge during hospitalization. The final 2 points were because of
cases in the literature associated with
clopidogrel.

DISCUSSION

Clopidogrel is widely used for pa-
tients with acute coronary syndrome.
When combined with aspirin, it is the
first-line antiplatelet therapy for decreas-
ing cardiovascular events.\(^1\)\(^3\) It is also ad-
ministered when a stent-assisted coiling
placement is envisioned; then, aspirin,
81 mg once daily, and clopidogrel, 75
mg once daily, are given for at least 3 to
5 days before the procedure, or a loading
dose of clopidogrel, 300 mg once, may
be administered before a procedure.\(^4\)

Clopidogrel is an antiplatelet agent
belonging to the thienopyridine class
that has widely replaced ticlopidine be-
cause of its superior safety profile. It has
a wide variety of side effects, the most
common being bleeding, diarrhea, rash,
indigestion, nausea, and vomiting.\(^5\) It is
also associated with more severe adverse
reactions like pancytopenia, thrombotic
thrombocytopenic purpura, hepato-
toxicity, serum sickness, and systemic
inflammatory response syndrome.\(^6\)\(^1\)\(^3\)

In terms of hepatotoxicity, the most
common observation was a mixed hepa-
tocellular and cholestatic pattern, with
tree cases of isolated hepatocellular
injury and one of cholestatic injury.\(^14\)
Review of the literature suggested only
a few cases of hepatotoxicity caused by
clopidogrel.

Clopidogrel undergoes activation by
hepatic metabolism by CYP3A4 and
CYP3A5. Simultaneous administration
of CYP3A4 inhibitors like ketoconazole
was shown to prevent the metabolism
and reduce the toxicity of clopidogrel.
High CYP3A4 activity is an important
risk factor for induction of clopidogrel-
induced hepatotoxicity.\(^15\)

The mechanism of clopidogrel-in-
duced liver injury is either direct dose-
dependent toxicity or dose-independent
CASE STUDY

An Idiosyncratic Reaction to Clopidogrel

idiosyncratic hypersensitivity reaction. Our patient had onset of symptoms within five days of initiation of the medication, probably indicating a hypersensitivity mechanism. The patient's other home medications were a stable regimen for years. Secondly, the patient received the anesthetic propofol, which has been very rarely associated with hepatitis; when it is associated with hepatitis, a hepatocellular pattern is more prevalent. However, a supporting drug challenge and a positive drug rechallenge highly favor the diagnosis of clopidogrel-induced hepatotoxicity.

Our patient had resolution of symptoms and improvement of liver function within 24 to 48 hours of the discontinuation of the medication. Even though acute liver injury is rare with clopidogrel, it is important for clinicians to recognize that this medication is potentially hepatotoxic. Thus, it should be used with caution in patients with underlying liver disease and should be discontinued if signs of jaundice or overt liver failure are observed.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Acknowledgements

The authors wish to thank Jim Kelley, PhD, from the Department of Internal Medicine, Quillen College of Medicine, East Tennessee State University, Johnson City, for assistance in writing. Leslie Parker, ELS, provided editorial assistance.

References

15. The Price Tag

The human’s “desire to take medicine” carries, however, a price tag.

Nature’s maladies are succeeded by iatrogenic hazards.

CASE STUDY

Pemphigus Vulgaris with Tense Bullae

Emilie T Nguyen; Shinko K Lin, MD; Jashin J Wu, MD

ABSTRACT

We report a case of a 51-year-old woman with a history of type II diabetes mellitus and dyslipidemia presenting with pain, swelling, and crusting of the lips. One year after onset of mucosal lesions, she developed an abdominal eruption with several tense vesicles and bullae on an erythematous base. The hematoxylin and eosin stain sample was consistent with a diagnosis of pemphigus vulgaris. The tense bullae of our patient highlight a rare phenotype of pemphigus vulgaris, which fits the mucocutaneous type because of involvement of the oral mucosa, with the exception of the findings of tense bullae.

CASE REPORT

A 51-year-old woman with a past medical history of type II diabetes mellitus and dyslipidemia presented to the Dermatology Department with pain, swelling, and crusting of the lips. This was accompanied by anal pain, odynophagia, and weight loss of 20 kg since the onset of symptoms. Previous evaluations by Head and Neck Surgery, Allergy, and Infectious Diseases Departments included lip biopsy, viral and bacterial cultures, and treatment with topical antifungals, an oral antiviral, topical and oral antibiotics, and topical steroids. The biopsy and culture studies did not reveal the etiology of her condition, and the treatments did not improve her symptoms.

One year after onset of her mucosal lesions, the patient developed an abdominal eruption consisting of several tense vesicles and bullae on an erythematous base (Figure 1). She also had lip edema and crusting, oral erosions and ulcerations, and an anal fissure. Histologic examination revealed suprabasal acantholysis (Figure 2), the histologic hallmark of Pemphigus vulgaris (PV) that is essential for diagnosis. Furthermore, direct immunofluorescence showed intercellular staining with immunoglobulin G (IgG) and complement test C3, which was also consistent with PV.

After biopsy, the patient was empirically started on methylprednisolone, 48 mg daily. After confirmation of her diagnosis, the patient was also started on mycophenolate mofetil, 500 mg twice daily. The methylprednisolone was later switched to prednisone, 80 mg daily, because of gastrointestinal intolerance. Owing to minimal response after 2 months of therapy, the patient received 2 rituximab infusions of 1000 mg, 2 weeks apart. There was noticeable improvement within 2 weeks of her first dose of rituximab.

DISCUSSION

PV is an autoimmune disease with the average age of onset between 40 and 60 years of age. It is characterized by involvement of the oral mucosa, such as painful oral erosions that often precede painful, cutaneous flaccid vesicles and bullae. Involvement of the oral mucosa is usually accompanied by severe pain that can lead to weight loss and malnutrition. Although it is a rare disease, with incidence rates between 0.1 and 0.5 per 100,000 people per year, PV has the potential for life-threatening complications, and treatment is always indicated at the time of disease onset.

PV can be further subdivided into mucosal dominant type, presenting with mucosal lesions and minimal skin involvement; and mucocutaneous type, which presents with skin blisters and erosions along with mucous membrane lesions. IgG antibodies against desmoglein (Dsg) 1 and Dsg 3, cadherin-type cell-to-cell adhesion molecules in desmosomes, are believed to play a role in inducing vesicle and bullae formation in PV. The dysfunction in Dsg 1 and Dsg 3 results in the loss of cell-to-cell adhesion in skin membranes and mucous membranes, respectively.
CONCLUSIONS

This case is of special interest because of the findings of tense, rather than flaccid, bullae (Figure 1). To our knowledge, there has been only one other case reported of PV with tense bullae with suprabasal acantholysis but no evident mucosal involvement, which Yoshida et al\(^5\) described as cutaneous-type PV. Cutaneous-type PV, which has yet to be categorized as a third type of PV, is thought to be a transient phenotype evolving from the previously described subdivisions of PV.\(^4\) To date, there have been seven reported cases of putative cutaneous-type PV.\(^6\) The tense bullae of our patient highlight a rare phenotype of PV that fits the mucocutaneous type caused by involvement of the oral mucosa, with the exception of the findings of tense bullae.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

References


The Whole Man

Medicine alone takes as its province the whole man … It is concerned with … man in all the complexity of his body and mind from his conception to his last breath; and its concerns extend increasingly beyond his sicknesses, to the conditions which make it possible for him to lead a healthy and happy life.

—Walter Russell Brain, 1st Baron Brain, 1895-1966, British neurologist and author of Brain’s Diseases of the Nervous System
CASE STUDY

Adult Intussusception

Teng Lu, MD; Yi-mei Chng, MD

INTRODUCTION

The clinical presentation of intussusception in adults can be nonspecific, with the “classic” triad of abdominal pain, vomiting, and currant-jelly stools found in children rarely seen, leading to delays in diagnosis. Nevertheless, intussusception is an important differential to consider because most cases in adults are caused by structural lesions, commonly malignant neoplasms. In contrast to pediatric intussusceptions, which are managed nonoperatively with air contrast enemas, treatment in adults is exploratory laparotomy for surgical reduction or resection.

CASE REPORT

A 37-year-old man presented to the Emergency Department with cramping peri-umbilical abdominal pain, associated with multiple episodes of nonbloody emesis. He reported similar episodes occurring several times a year for the previous 5 years. Previous episodes had resolved after receiving antiemetics and narcotics in the Emergency Department. He also reported one episode of dark tarry stools 4 months earlier. At that time, his primary care physician ordered contrast computed tomography (CT) of the abdomen and pelvis that showed loops of small bowel with diffuse wall thickening and mild dilatation, possibly indicative of an early inflammatory process. Review of systems was negative for fevers, weight loss, ocular symptoms, oral ulcers, skin lesions, joint pain, or diarrhea. He was otherwise in good health, with the only medications being levothyroxine and omeprazole. He had had no abdominal surgeries. His family history was significant for Crohn disease in his mother.

On physical examination the patient was a well-developed man in moderate discomfort, holding his abdomen with knees drawn up to his chest. He had a temperature of 98.8°F (37.1°C), pulse of 84 beats/min, blood pressure of 132/82, respiration of 20 breaths/min, and oxygen saturation of 97% on room air. His heart had a regular rate and rhythm, and his lung sounds were clear. Despite his apparent discomfort, his abdomen was soft and nondistended with normal bowel sounds. He had mild tenderness of palpation in the left upper quadrant with no obvious palpable masses.
He was hemoccult negative with brown stool. His genitourinary exam was normal.

Laboratory tests were unremarkable, showing a white blood cell count of 11.2 K/μL (normal range, 3.5-12.5 K/μL), and hematocrit of 45.9% (normal range, 34%-46%). Electrolytes, liver function test results, and pancreatic enzymes were all within normal limits. Given his persistent discomfort on serial exams unrelieved by antiemetics and narcotics, an abdominal CT was performed. The CT scan showed a nonobstructive small-bowel intussusception within the proximal small bowel (Figure 1).

General Surgery was consulted and the patient was taken to the operating room for exploratory laparotomy. The entire bowel was inspected from the ligament of Treitz to the terminal ileum. No intussusception was noted, but the patient was found to have a 20-cm segment of mildly thickened, boggy proximal jejunum, as well as mild creeping fat along the terminal ileum without inflammation. Given no evidence of active intussusception, mass, stricture, or bowel ischemia, no bowel resection was performed. The patient was discharged home on postoperative day 2. He was referred to gastroenterology for follow-up tests to evaluate for Crohn disease.

During the following year, the patient returned to the Emergency Department two more times for cramping abdominal pain. Both times he had CT scans that did not show recurrent intussusception or other acute pathology, and he was discharged home after symptoms were controlled. It was suspected that there may have been a secondary gain component to his subsequent encounters for abdominal pain, though mild inflammatory bowel disease could not be excluded. He had outpatient upper endoscopy and colonoscopy that were both unremarkable, with no ulcers, polyps, granulomas, or masses noted. Random biopsies of the stomach showed mild chronic inflammation without evidence of *Helicobacter pylori*. Random biopsies of the duodenum, terminal ileum, and colon showed no histologic abnormalities. He has been referred for capsule endoscopy in the future to further investigate the small bowel for evidence of Crohn disease.

**DISCUSSION**

Intussusception involves the telescoping of a segment of bowel into an adjacent segment, leading to obstruction, inflammation, and possible ischemia. Although intussusception is the leading cause of intestinal obstruction in children, it is relatively rare after childhood, accounting for less than 5% of bowel obstruction in adults. Adult intussusception occurs most often in the small bowel and is classified on the basis of location. It can be categorized as enterotentric (small bowel only), colocolic (large bowel only), ileocolic (terminal ileum prolapses within the ascending colon), or ileocecal (ileocecal valve is the lead point). In a study of 745 surgically diagnosed adult intussusceptions, 52% were found in the small intestine (39% enterotentric, 13% ileocecal) and 38% in the large intestine (17% ileocecal, 17% colocolic, 4% appendiceal).

In contrast to intussusceptions in children, which are typically primary or idiopathic, most adult intussusceptions are caused by a structural lesion. A significant proportion of these lead points are malignant neoplasms, accounting for 66% of colonic intussusceptions and 30% of cases in the small intestine. Adenocarcinoma is the most common malignant lead point in the colon, whereas metastasis is the most common malignant lead point in the small intestine. Other etiologies include benign tumors (adenomatous polyps, lipomas, fibromas, leiomyomas, hamartomas), adhesions, lymphoid hyperplasia, cystic fibrosis, scleroderma, celiac disease, inflammatory bowel disease, appendicitis, pancreatitis, and rectal foreign bodies. Sixteen percent of small-bowel and 5% of large-bowel intussusceptions are idiopathic.

The clinical presentation of intussusception in adults can be variable, posing a challenge to diagnosis. The “classic” pediatric presentation of abdominal pain, bloody currant-jelly stools, and palpable tender abdominal mass, seen in 15% of pediatric intussusceptions, is rarely seen in adults. In contrast to intussusception in children, adult intussusceptions often present as chronic intermittent cramping abdominal pain associated with nonspecific signs of bowel obstruction including nausea, vomiting, gastrointestinal bleeding, constipation, or abdominal distention. One surgical series of 58 adults noted that intussusceptions with malignant etiologies were more likely to have hemoccult-positive stools and tended to occur in older populations.

Abdominal CT is now widely regarded as the modality of choice for diagnosing intussusceptions in adults. The CT finding of a heterogeneous “target” or “sausage-shaped” soft-tissue mass consisting of an outer intussusception and central intussusceptum is virtually pathognomonic. Mesenteric fat and vessels are often visible within the bowel lumen, and varying degrees of proximal bowel dilatation may be present. In a retrospective review of 33 adult patients with intussusception, 30 were diagnosed by CT, and those caused by neoplastic processes were more likely to be associated with other signs and symptoms of obstruction. Other imaging modalities include plain abdominal films that can provide clues regarding site of obstruction but are neither sensitive nor specific in terms of diagnosis. Ultrasound is a helpful tool especially in children; it can be useful in adults when an abdominal mass can be palpated but may be limited by body habitus and the presence of air in distended bowel loops.

Management of symptomatic adult intussusceptions traditionally involves exploratory laparotomy or laparoscopy followed by resection of lead point masses or areas of ischemia. Preoperative reduction by barium or air, or manually in the operating room is generally not recommended owing to theoretical risks of perforation, seeding of microorganisms or tumor cells, and increased surgical complications of manipulated friable and edematous bowel. However, preoperative reduction can be considered in consultation with a surgeon in cases where a diagnosis of benign lesion has previously been established and the bowel involved is viable, or where resection may result in short gut syndrome. Of note, nonobstructing intussusception detected incidentally on CT in an otherwise asymptomatic patient does not require intervention.

With regard to operative management, recent studies recommend a selective approach to bowel resection that takes
Adult Intussusception

into consideration the location and pathologic characteristics of the underlying lesion.11,12 In patients older than age 60 years or in intussusceptions with colonic lesions, bowel resection following the appropriate oncologic principles is recommended given the high incidence of malignancy.6 In cases of transient small-bowel intussusceptions in the setting of benign etiologies such as celiac sprue or Crohn disease, resection may not be warranted because treatment of the underlying disease process should improve symptoms. Given the significant risk of short gut syndrome in patients with Crohn disease (5%-10%), aggressive resection therapy may not be indicated if the bowel involved is healthy without evidence of obstruction or ischemia.13 These factors were likely taken into consideration in the decision not to perform bowel resection in the patient presented in this case.

CONCLUSION

Although intussusception is a rare cause of abdominal pain in adults, it is an important diagnosis to consider in patients with recurrent abdominal pain because it may be a harbinger of malignancy. Symptoms can be nonspecific, and diagnosis is best made by CT imaging. Management is often surgical, and delays in diagnosis can lead to complications such as bowel obstruction, ischemia, or undiagnosed malignancy. Prognosis is generally favorable depending on the etiology of disease, with poorest outcomes in small-intestinal intussusceptions caused by metastatic disease.7

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

Acknowledgment
Mary Corrado, ELS, provided editorial assistance.

All the Manner and Degrees

As no two persons are exactly alike in health so neither are any two in disease; and no diagnosis is complete or exact which does not include an estimate of the personal character, or the constitution of the patient. … for to treat a sick man rightly requires the diagnosis not only of the disease but of all the manner and degrees in which its supposed essential characters are modified by his personal qualities, by the mingled inheritances that converge in him, by the changes wrought in him by the conditions of his past life, and by many things besides.

— Sir James Paget, 1st Baronet of Harewood Place (Middlesex), 1814-1899, English surgeon and pathologist, best known for Paget disease

References
Echocardiogram for Pericardial Effusion

Joseph Gascho, MD

Was it by accident they found it—
another test for other woes?
Now they want to know how big it is,
and if it keeps the heart from filling full
with each diastole.

I see an inch of fluid on every side.
It grew so gradually, I would guess
you never knew. Your heart as always,
goes about its tick-tock duties,
ever knowing something’s wrong.

I wonder if they’ll stick a needle in,
suck some fluid out, to see
just what the stuff’s made of—
or maybe play a waiting game,
repeat this sonogram a month from now.

There was a time, if it was me,
I’d have begged them
to pierce my chest so I could know.
To know is good,
my doctor teachers always said.
But now I’d tell them no.
Ignorance may not be bliss,
but knowledge never is complete.
Learn one fact, only to find
you must make another choice.
Another thing you didn’t know you didn’t know.

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Hershey College of Medicine in PA. E-mail: jgascho@hmc.psu.edu.
CASE STUDY

A 13-year-old boy had fever, fatigue, and breathlessness for two weeks before presenting to the Emergency Department. He also had painless lymphadenopathy on both sides of his neck, axilla, and groin. Four hours before presentation to the Emergency Department, he developed drooping of the right upper eyelid. There was complete ptosis and no associated diplopia. The pupil of the right eye was dilated and nonreactive. The extraocular movements and pupil of the left eye were normal. There was no headache, vomiting, or seizures. Two hours after presentation the patient developed sudden-onset complete weakness of the left side of his body along with left upper motor neuron facial palsy. With a clinical diagnosis of acute cerebrovascular accident, an urgent noncontrast computed tomography scan of the head was performed. It showed multiple hemorrhages, one of which was located in the ventral midbrain on the right side (Figure 1), possibly explaining the contralateral hemiplegia and ipsilateral oculomotor palsy.

Investigations revealed hyperleukocytosis (454,000/µL), hemoglobin of 9.2 g/dL, and thrombocytopenia (42,000/µL), with greater than 99% lymphoblasts and many degenerated cells seen in the peripheral smear examination (Figures 2 and 3). Prothrombin time and activated partial thromboplastin time were 13 seconds and 37 seconds, respectively (reference value 12 seconds and 35 seconds, respectively). Fibrinogen concentration was 2.5 g/L, and there was no laboratory finding to suggest disseminated intravascular coagulation. Renal and liver functions were normal. Serum lactate dehydrogenase was elevated (9 times the upper limit of the reference value). Serum potassium was 6 mmol/L, but there were no accompanying electrocardiographic abnormalities of hyperkalemia. Serum calcium was 9.3 mg/dL, whereas serum uric acid was elevated to 11.4 mg/dL.

We diagnosed acute leukemia, probably acute lymphoblastic leukemia (ALL), on the basis of peripheral blood film. Tumor lysis syndrome was suspected and the patient was hydrated well. Emergency leukapheresis was planned in view of hyperleukocytosis and breathlessness. But before we obtained additional samples for flow cytometry to confirm the diagnosis and before the initiation of leukapheresis, the patient developed seizures, after which he became comatose and died. Clinical course suggested a possible fatal intracranial hemorrhage as the preterminal event.

DISCUSSION

Neurologic manifestations in patients with leukemia can have multiple etiologies, depending on whether the time of presentation is pre- or postchemotherapy. In prechemotherapy, intracranial hemorrhage and leukemic infiltration are the important causes of neurologic symptoms, whereas in postchemotherapy, infections are the most important cause.1,2 In children with ALL, neurologic manifestations can occur in up to 9% of cases, and in those patients with ALL with extreme leukocytosis (total leukemia blood cell count > 400,000/µL), 2% can have intracranial hemorrhage.3 In patients with acute leukemia, intracranial hemorrhage portends a poor prognosis, with a mortality rate approaching 19.7% in the first 72 hours and 32.7% at 30 days.4 Acute nonlymphoblastic leukemias present more commonly with intracranial hemorrhage than ALL and are more frequently fatal early in the course of the disease (7% in acute myeloblastic leukemia vs 1% in ALL in one series).5,6

Brain stem strokes or cerebrovascular accidents are relatively uncommon, particularly in children. Midbrain strokes commonly result from ischemia or hemorrhage as in any other cerebrovascular territory. Though both
ischemia and hemorrhage can lead to stroke in children, the latter seems to be a more important cause in children with cancer and leukemia.\textsuperscript{2,8} Eponymous syndromes of brainstem strokes are often heard but seldom seen. The presence of ipsilateral oculomotor palsy and contralateral hemiplegia constitutes Weber syndrome. Weber syndrome occurs as a consequence of a lesion located in the cerebral peduncle of the midbrain, which includes the pyramidal fibers (causing contralateral hemiplegia) and the third nerve fascicle (causing ipsilateral oculomotor paresis).\textsuperscript{9} This patient’s neuroimaging demonstrates a strategically located small bleed in this region of the midbrain, which correlates with the clinical presentation. We undertook a systematic search of PubMed for similar cases. Search terms for our PubMed searches are listed in the Sidebar: PubMed Search Terms. We found that the index case was the first case of leukemia reported in the literature to have presented clinically as Weber syndrome.

Presence of hyperleukocytosis, thrombocytopenia, and acute promyelocytic leukemia are well-known risk factors for hemorrhage in leukemia.\textsuperscript{10} Acute promyelocytic leukemia is the most common leukemia to be associated with a deranged coagulation profile and hemorrhagic manifestations.\textsuperscript{11,12} Hyperleukocytosis (with subsequent intracranial bleeding) is more common in ALL patients with translocations involving the chromosomal abnormalities t(4;11) (q21;q23) and t(9;22)(q34;q11) (Philadelphia-positive ALL).\textsuperscript{13,14} In treatment-naive leukemia patients, bleeding related to hyperleukocytosis has been noted to be one of the most important causes of death.\textsuperscript{1} The use of L-asparaginase may also be a cause of intracranial hemorrhage in leukemia patients receiving chemotherapy.\textsuperscript{15} Our patient had hyperleukocytosis and thrombocytopenia, both of which could have predisposed him to intracranial hemorrhage.

Hyperleukocytosis (usually defined as a white blood cell count > 100,000/µL) generally results in leukostasis, wherein intravascular accumulation of leukemic or nonleukemic white blood cells results in various clinical manifestations, particularly respiratory distress and neurologic disturbances. Hyperleukocytosis is a medical emergency; its management includes supportive care (hydration, prevention, and treatment of tumor lysis syndrome) and urgent cytoreductive therapy. Cytoreduction may be achieved by hydroxyurea, leukapheresis, or conventional chemotherapy.\textsuperscript{16} Despite such aggressive measures, mortality remains high in these patients, especially in those with intracranial hemorrhage. Though leukapheresis may reduce circulating lymphoblast cells, thereby effectively controlling leukostasis in cerebral circulation, it has not been consistently shown to improve outcomes.\textsuperscript{16} The approach in patients with thrombocytopenia and leukostasis who are at risk of intracranial bleeding should be to identify the type of leukemia as early as possible. Provision of leukapheresis, platelet transfusion, and cytoreductive agents, along with appropriate chemotherapy, may improve outcomes.\textsuperscript{16}

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

References

PubMed Search Terms

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Image Diagnosis: Weber Syndrome: A Rare Presentation of Acute Leukemia—A Case Report and Review of the Literature


Waterworks

The physics of a man's circulation are the physics of the waterworks of the town in which he lives, but once out of gear, you cannot apply the same rules for the repair of the one as of the other.

— Aequanimitas, with Other Addresses, Sir William Osler, MD, 1849-1919, physician, clinician, pathologist, teacher, diagnostician, bibliophile, historian, classicist, essayist, conversationalist, organizer, manager, and author
ABSTRACT
As health care reform in the US evolves beyond insurance reform to encompass delivery system reform, the opportunity arises to harness the Affordable Care Act to strengthen patient care in America. One area for dedicated individuals to lead this effort is by improving transitions in patient care across the continuum of team members, specialties, settings, and systems. This article will describe innovations of the surgicalist and acute care surgeon that have emerged in response to the challenges facing surgery in specialization, geography, and the need to comply with health care reform mandates. Three ways will be described to integrate these innovations with pilot programs in the Affordable Care Act: to promote teamwork, to reduce readmissions, and to strengthen emergency care because the key location where the joint efforts intersect most acutely with patient need is in our nation’s Emergency Departments.

CONTRIBUTIONS AND INSIGHTS IN TEAMWORK FROM THE AMERICAN COLLEGE OF SURGEONS
The American College of Surgeons (ACS) has a long history of successful multidisciplinary collaborations to enhance patient safety. The ACS spearheaded the creation of the Joint Commission,1 developed the guiding principles of Advanced Trauma Life Support, worked with emergency medical services agencies to coordinate the prehospital trauma response and certification of Level I trauma centers, and pioneered the National Surgical Quality Improvement Program. A key partner for success is the Association of American Medical Colleges (AAMC), whose record of accomplishment and vision are consistent with the ACS’s intent to optimize the quality and safety of patient care nationally. In spring 2014, the AAMC Health Workforce Research Conference explored expanded roles for community providers—medical care providers who serve predominantly low-income or medically underserved populations. The Affordable Care Act (ACA)2 (ACA) has required that covered plans in state insurance exchanges include adequate networks of community providers, who may assume a key future role in team collaborations with the ACS.

In 2009, the ACS issued a statement on high-performance teams and recognized that safe and optimal patient care requires the contributions from many health care professionals across disciplines working together perioperatively.3 A challenge is that the surgeon must function both as a leader and as a member of the high-performing team. The ACS recognizes several key attributes of successful teams: a commitment to the best interest of the patient; respectful behaviors toward team members; constructive conflict resolution; and leadership that is clearly defined, is appropriate to the circumstances and solicits input to achieve team-based coordinated decision making. Other keys to success are clear communication with verification of understanding, structured handoffs throughout the phases of care, and the ability to be flexible and adaptable to changing situations.

THE SURGICALIST AND ACUTE CARE SURGEON EMERGE TO RESOLVE THE EMERGENCY CARE CRISIS
A series of 3 reports from the Institute of Medicine in 2006 detailed a national crisis in emergency care, including overcrowding in the Emergency Department (ED) and the hospital, ambulance diversion, and the boarding of admitted patients in the ED.4 From the surgical perspective, a major contributor to this crisis has been the national workforce shortage in surgery, which has been exacerbated by a shortage of inpatient hospital beds and inadequate hospital and nursing staffing. The needed services of surgeons are under stress because there are more limited numbers of these professionals who are qualified to provide operative care. In addition, the percentage of general and trauma surgeons comprising the total health care workforce has steadily declined by 50%, from 8% in 1975 to just over 4% in 2005.5 A projected surplus of physicians and budgetary pressures in the 1990s resulted in graduate medical education funding being frozen at 1996 levels with the passage of the 1997 Balanced Budget Act.6 This capped the number of residency spaces, resulting in only about 1000 general surgery chief residents graduating each year, a number similar to that in the 1970s. Because nearly 70% of these graduates specialize in surgery,5 any fallback to surgical training is unlikely to meet the supply and distribution targets. These factors, in combination with a trend toward earlier retirement by surgeons and a greater-than-expected rate of growth of the US population, have led to AAMC projections that there will be a shortage of 46,000 surgeons and medical specialists in the next decade7 to meet the increasingly complex needs of an aging population. In response, the AAMC has led important efforts to address immediate and long-term workforce needs.
efforts to increase both the number of graduating medical students nationally (by expanding medical school class sizes) and the number of residency training positions in the surgical specialties.

Across the nation, EDs have struggled to identify general and trauma surgeons and surgical specialists willing to take emergency call, a factor contributing to the decline in the number of hospital-based EDs in rural areas in the US by 27% between 1990 and 2009.\(^9\) A study in the *Journal of the American Medical Association* in 2011 concluded that for-profit ownership, safety-net status, location in a competitive market, and low profit margin were associated with an increased risk of ED closure.\(^8\) The crisis is most severe in rural America, where there are nearly 1200 counties without a general surgeon available.\(^9\) Careful planning will be necessary to better distribute the nation’s precious resources. In some parts of our country, one can drive through health care “deserts” for hundreds of miles and not see an ED, whereas in some cities one can walk out of one Level I Trauma Center into another one a few blocks away.

Recent trends, however, provide reasons to be optimistic. Over the past few years, our nation has witnessed the emergence of billboards and commercials that advertise short waiting times in certain EDs, and new online programs allow patients to wait at home until an ED bed is available for them. These changes suggest that the delivery of ED care is becoming competitive, and they offer a starting point from which to coordinate emergency care in urban and rural areas and to increase the number of ED centers in rural America.

Another opportunity arises from the innovations of the surgicalist and the acute care surgeon, which have emerged to reinvigorate trauma and emergency general surgery. These occupations share the core concept of a surgeon dedicated to evaluate patients in the ED and hospital. The 2 fields have emerged as a new career for recently trained surgeons,\(^10\) and as of 2012, an estimated 400 programs exist across America.\(^11\) The innovations offer a platform for surgeon partnerships with ED physicians, critical care physicians, physician extenders, and other surgical specialists to improve care. One example of a fruitful collaboration has been with anesthesiologists\(^12\) and internists\(^13\) to characterize the impact of smoking on surgical outcomes, leading to the recommendation that active smokers undergo smoking cessation counseling before undergoing elective surgery.

Since 2010, at least three major events in trauma and emergency surgery have underscored the importance of sustaining the emergency care system. The first was the favorable recovery of Congresswoman Gabrielle “Gabby” Giffords after being shot in 2011 in Tucson, AZ, which catalyzed a positive change in perception about the heroism of emergency medicine physicians and trauma surgeons.\(^14\)

The second event was the response in Massachusetts to the Boston Marathon bombings in 2013, especially the lifesaving treatments by the Acute Care Surgery and Emergency Medicine programs at Massachusetts General Hospital and Beth Israel Deaconess Medical Center, both in Boston.\(^15\) The ability of the Boston hospitals to care for the surge of 200 extra patients highlights the quality and importance of emergency medical services.

The third event came in 2013 after the Asiana Airline crash in San Francisco, CA, when nearly 200 patients with a variety of neurosurgical, orthopedic, burn, and trauma injuries were treated at 12 San Francisco Bay Area hospitals.\(^16\) Ultimately, identifying ways to support those courageous providers willing to place themselves on the clinical front lines will be key to solving the emergency care crisis.

### The Affordable Care Act: Opportunities Across Specialties and Systems to Reform the Delivery System

As the ACA evolves, three areas present themselves in which collaborations across systems and health care professionals may lead to new solutions to both improve patient care and resolve the emergency care crisis. First, greater collaboration will be required to fulfill the overarching intent of accountable care organizations (ACOs), which are key to the financial viability of the ACA. It will be essential to first strengthen the coordination between ACOs with community providers and medical homes (another innovation championed by the ACA). A special opportunity then arises to connect these efforts with dedicated hospital-based programs such as surgical hospitalists and acute care surgeons. Novel collaborations could promote patient throughput in the hospital in the following ways: by shortening waiting times for surgery, decreasing the turnover time for operating rooms, improving time-outs, enhancing communication with primary care physicians, implementing preoperative guidelines to reduce operating room cancellations and improve preoperative preparedness, and assisting with discharge planning to shorten the length of stay.

Perhaps ACOs could also be directly tasked to solve ED overcrowding and boarding. In the United Kingdom, a successful policy, championed by Lord Ara Darzi, surgeon and former Parliamentary Under-Secretary of State in the Department of Health in the House of Lords mandated either patient admission or discharge home within four hours of arrival at an ED. The policy generated positive long-term results by ending patient boarding in ED hallways, shortening patient waiting times to be evaluated, and accelerating improvements in hospital capacity. However, the possible negative impact on health care staff and patient outcomes if organizational skills are inadequate must also be carefully balanced.\(^16\) Western Australia followed the lead of the United Kingdom and adopted the four-hour target, whereas New Zealand chose a six-hour target to complete ED patient evaluations. A similar ED policy could be piloted for ACOs in the US.

The second focus for collaborations should be to reduce hospital readmissions of patients who return for reevaluation in the ED. In 2013, as authorized by the ACA, the Centers for Medicare and Medicaid Services proposed a method and payment adjustment factors to account for excess hospital readmissions because of conditions including heart attack, heart failure, and pneumonia, known as the Hospital Readmissions Reduction Program.\(^17\) The Agency for Healthcare Research and Quality also spearheaded Project RED (Re-Engineered
Discharge), outlining 10 guiding principles for hospitals to employ to reduce the number of patient readmissions. ACOs should seek new solutions to minimize hospital readmissions, which might be achieved through the use of discharge coaches and teams, improved communications with primary care providers, standardization of processes, improved patient education, and an increased role for community providers in inpatient hospital care. New payment models penalize premature discharges that lead to readmission with reduced hospital reimbursement, providing another incentive for ACOs to innovate in this area. In 2014, Medicare fined more than 2600 US hospitals for having too many patients be readmitted to the hospital within a month for additional inpatient stays. A key to success will be to define the critical balance between increased readmission rates with shortened length of hospital stay, and to promote collaboration and communication with a patient-centered focus.

Third, the key principle of teamwork must be prioritized further to optimize efficiency and coordination. The ACS has identified four critical components to the success of multidisciplinary teams: 1) the use of team-based education and training; 2) an institutional commitment to providing opportunities for experiential learning, workflow, and feedback; 3) the monitoring of performance; and 4) rewards for good conduct and sanctions for noncompliant individuals. The health care field must carefully consider penalties for poor performance by team members, because the existing literature has demonstrated that pay-for-performance incentives have had minimal impact on improving patient outcomes. Perhaps there is much to be learned from the steps taken by the airline industry. One of the tools in transforming aviation to a culture of safety was the creation of checklists, a concept championed by Dr. Atul Gawande in his book, The Checklist Manifesto. This development of checklists served as the first step to define expectations of team performance, followed by the introduction of a National Transportation Safety Board (NTSB) to provide oversight and to enforce the checklists (including penalties for substandard performance). The NTSB was also charged to disseminate the knowledge gained through investigations of aviation accidents and system failures. When asked what he perceived as the key next step to transform health care, Captain Chesley “Sully” Sullenberger recommended the creation of a medical version of the NTSB.

The time has now arrived for health care to move beyond checklists and to introduce innovative partnerships to promote teamwork across the continuum of nurses, anesthesiologists, emergency medicine physicians, community providers, surgeons, and hospital leaders. One strategy to improve efficiency, promote conflict resolution, and enhance team building is through simulation, which is being used with increasing frequency in medical schools and postgraduate training programs. At a regional level, teamwork and collaboration across institutions will be key, because a single hospital will be unable to solve the national emergency crisis alone. The answer will require a vibrant community of health care professionals and emergency rooms working together, rather than competing against each other.

Another answer to the emergency care crisis in America is to inspire a new generation of surgeons to dedicate their careers to emergency surgical care by building on existing graduate medical education programs that provide federal support and loan forgiveness to graduates who practice in rural America. One proposal has been to create a General Surgery National Health Service Corps to deploy board-certified surgeons for 3-6-month rotations across rural America, particularly the 1200 counties without a surgeon available. A broader and innovative federal approach could also be similarly applied across medical specialties. Such an initiative would enable the US Congress to send coordinated teams of physicians across the country to achieve the objectives of ACOs in reducing hospital readmissions and in resolving ED overcrowding, boarding, and ambulance diversion.

One important question is, where may the funding to support these future collaborations be found? The answer is from the ACA itself, which recognized the importance of continued research in trauma and emergency care coordination, regionalization, and mass disaster preparedness, and authorized $224 million to fund the trauma and emergency medical services programs under the Public Health Service Act of the ACA. In his annual budget proposal requests, US President Barack Obama has not yet asked Congress for the appropriation of these funds, but perhaps recent natural events can remind both the President and Congress of the vital need to reprioritize funding within existing programs of the ACA to sustain our emergency care system. In the teams of dedicated health care professionals across the US, there is a special opportunity to collaborate to improve both quality and outcomes of care. Health care professionals can do this by fulfilling the promise of ACOs, reducing hospital readmissions, and improving coordination and teamwork to transform emergency care nationally and worldwide.

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Harnessing the Affordable Care Act to Catalyze Delivery System Reform and Strengthen Emergency Care in America


Humane

It behooves us to remember that medicine is, above all else, humane as well as human; that its beginning, middle, and end is to relieve suffering, and that whatever is outside this may indeed be science of some sort, but certainly not medicine.

—Alfred Stillé, 1813-1900, American physician and professor of medicine at the Pennsylvania Medical College
COMMENTARY

Agents for Change: Nonphysician Medical Providers and Health Care Quality

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ABSTRACT

Quality medical care is a clinical and public health imperative, but defining quality and achieving improved, measureable outcomes are extremely complex challenges. Adherence to best practice invariably improves outcomes. Nonphysician medical providers (NPMPs), such as physician assistants and advanced practice nurses (eg, nurse practitioners, advanced practice registered nurses, certified registered nurse anesthetists, and certified nurse midwives), may be the first caregivers to encounter the patient and can act as agents for change for an organization’s quality-improvement mandate. NPMPs are well positioned to both initiate and ensure optimal adherence to best practices and care processes from the moment of initial contact because they have robust clinical training and are integral to trainee/staff education and the timely delivery of care. The health care quality aspects that the practicing NPMP can affect are objective, appreciative, and perceptive. As bedside practitioners and participants in the administrative and team process, NPMPs can fine-tune care delivery, avoiding the problem areas defined by the Institute of Medicine: misuse, overuse, and underuse of care. This commentary explores how NPMPs can affect quality by 1) supporting best practices through the promotion of guidelines and protocols, and 2) playing active, if not leadership, roles in patient engagement and organizational quality-improvement efforts.

INTRODUCTION

A prospective physician assistant (PA) student applicant explains to the admissions committee that s/he would like to become a PA rather than a physician because s/he “wouldn’t have to worry so much about the administrative aspects of health care and could spend more time taking care of patients.” Although this patient-centered sentiment may be noble, it is a misconception of modern nonphysician medical provider (NPMP) practice, including the roles of PAs, nurse practitioners, advanced practice registered nurses, certified nurse midwives, and certified registered nurse anesthetists. NPMPs, along with all other members of a patient’s health care team, are increasingly asked to take on administrative and quality aspects of health care delivery that once were the sole concerns of supervising physicians or administrators. NPMPs can and should play a major role in shaping health care quality and outcomes. These medical providers can do so readily by educating staff, promoting adherence to clinical guidelines and protocols, playing active roles in quality-related decision-making processes for their organizations, and leading patient-engagement efforts aimed at quality improvement. NPMPs are especially appropriate members of the health care team to strengthen and uphold best practices owing to their advanced knowledge base and to their role in enhancing physician trainees’ education. Furthermore, their training model and scope of practice are most often based on a collaborative approach to care, a paradigm of value in health care, and they often are able to expand the amount of care offered by a physician or medical service. The new paradigm may be that quality is everyone’s business—all staff at all hours—and NPMPs can be an effective agent for change in many settings owing to their training and highly visible role in health care delivery.

Health care quality improvement (QI) is a concern in many settings: outpatient and inpatient care; for individual patients and for public health; and in the context of specific illnesses, disciplines, product lines, and institutions. At the federal level, there has been a recent surge of support for improving health outcomes and patient satisfaction and allocating resources accordingly. As part of the 2009 economic stimulus package, the federal government dedicated $1.1 billion to study the effectiveness of medical modalities in curbing costs and improving quality for health consumers. Action steps aimed at improving quality in health care require shifts in an organization’s culture and in health care workers’ attitudes and a reworking of roles and processes. Mandates for QI now come from health reform legislation and professional certification bodies, and marketing influenced by consumer opinion has an impact as well. The PA maintenance of certification process, for example, now requires demonstration of participation in quality- and performance-improvement projects as well as continuing education credits during the ten-year recertification cycle. The emphasis on defining and improving health care quality delivered by the fractionated American system of care has increased the pressure on administrative and quality aspects of health care delivery. The federal government dedicated $1.1 billion to study the effectiveness of medical modalities in curbing costs and improving quality for health consumers.
on those very fractions to alter practices and communications to improve patient outcomes. This is congruent with many aspects of the unfolding health reform measures mandated by the Patient Protection and Affordable Care Act.17

Why are NPMPs of particular interest? As the population ages, there will be an increased need for medical practitioners. The Bureau of Labor Statistics projects 38% growth in the number of PAs and 31% growth in the number of nurse practitioners, certified nurse midwives, and certified registered nurse anesthetists for 2012-2022.18 These NPMPs diagnose conditions and counsel and treat many patients in many settings, including primary care and acute care settings, and the results are usually comparable to physicians and include high rates of patient satisfaction.19-21 Furthermore, the PA-physician practice model, for example, stipulates that a team approach be used when caring for patients. This model maintains clinical service stability and promotes optimal outcomes for patients.22 This practice architecture, coupled with growing support and utilization of collaborative care using interprofessional communication and practice models, can help to optimize the delivery of care.23-25

In Crossing the Quality Chasm, the Institute of Medicine emphasizes three problem clusters in the delivery of health care: misuse, overuse, and underuse of care.12 These problems can be avoided by gaining knowledge of and adhering to evidence-based clinical care guidelines (or consensus statements) published by authoritative, professional medical bodies26,27 and by using evidence-based clinical care protocols for select processes.28-29 Despite the national emphasis on the importance of clinical guidelines, adherence to guidelines in medical practice is often poor.30 Practicing physicians require extensive medical knowledge, but they may lack awareness of or be unfamiliar with the most recent guidelines or other evidence-based practices.31 This is an opportunity for NPMPs to add value to a medical practice or hospital service. They are well trained in the basic and clinical sciences and can play a key role in guiding health care staff in adherence to the most recent and relevant developments in evidence-based care. For example, they can thoroughly understand recent guidelines for target blood glucose levels in acute care settings, teach them to relevant staff, and oversee the monitoring. This adherence, driven by the NPMP, can be the cornerstone of a service’s or practice’s success in maintaining acceptable patient outcomes.32 Table 1 illustrates the triple C approach to optimal dissemination of clinical care guidelines and protocols using the NPMP as the change agent.

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<th>Table 1. Triple C approach for nonphysician medical providers’ role in promoting clinical care guidelines/protocols</th>
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a Guidelines are often published in consensus statements or on society Web sites.

NONPHYSICIAN MEDICAL PROVIDERS CAN AFFECT QUALITY OF CARE

Health care quality can be assessed as objective, appreciative, and perceptive,32 and NPMPs can affect these quality aspects in positive ways. Figure 1 details three ways NPMPs can play active roles that affect the three aspects of quality. Objective quality has historically been the province of those working in the QI Department or administrators of a health care organization. External regulatory standards (eg, those set by the Joint Commission or the Centers for Medicare and Medicaid Services) or established internal criteria set by the health care organization itself steer objective quality goals. Examples of quality goals can be found in documentation by the Surgical Care Improvement Project33 and the Consumer Assessment of Healthcare Providers and Systems,34 and they are tied to reimbursement structures for health care services. NPMPs’ active role in continually educating and updating other health care staff on developments in evidence-based practices can critically affect patient health outcomes (Table 1).

Appreciative quality is judged by colleagues and peers working in a similar setting. NPMPs can affect this aspect of quality by serving actively, even in leadership capacities, on organizational quality committees. Appreciative quality is less quantitative and more subjective (ie, opinion based on experience), but it may affect referral to providers and health care organizations.35 For example, a provider or organization that is known to provide exemplary care in concert with best practices is likely to have the opportunity to care for more patients, because more patients will be referred to them. In contrast, poor processes or outcomes, as judged by others in the same or a similar field, can be detrimental to reputation and revenue. Reputation and revenue are major considerations for any health care organization or provider delivering care under both for-profit and not-for-profit business models. Achieving good patient outcomes and discharging satisfied patients to the community is the best way to manage external appreciation of organizational quality. Internally, an organization can also enact a peer-satisfaction review process.36 By assuming membership and leadership on an organization’s quality-related committees, NPMPs will be at the table to represent their respective services, disciplines, and practices. Their perspective is not always appreciated in health care operations, but their involvement has been shown to enhance care processes.37 Furthermore, such collaboration in organizational quality initiatives can also affect objective quality concerns.
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COMMENTARY

Agents for Change: Nonphysician Medical Providers and Health Care Quality

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The idiom “Vote with your feet” illustrates perceptive quality, an aspect of quality with a role for NPMPs (Figure 1). Patients and family members, when not satisfied with their health care or provider, may have the option of switching providers. Patients often have strong opinions about the care they receive, and these opinions are not always based on objective data (e.g., Was the treatment effective?). How patients feel the care was delivered may be just as important as the treatment’s effectiveness from a customer service standpoint. In customer service industries—including health care—satisfied customers tell others, but dissatisfied customers tell many more. Dissatisfaction is communicated both informally, such as telling a friend or neighbor, and formally, via health consumer surveys by the Consumer Assessment of Healthcare Providers and Systems, for example.43 Therefore, leadership in patient engagement is an important potential role for NPMPs. The history of the NPMP as patient advocate, when coupled with the QI mandate, highlights the ideal role of the NPMP in patient engagement.39,40

Quality issues must be investigated, including patient or family interviews, with professionalism, attention to detail, advanced medical knowledge, and organizational awareness. A useful technique employed by one of the authors (NAB) is a brief quality conversation (Figure 1) with patients or families, where the focus is on assessing satisfaction with current care and determining what manageable solutions might be offered. If patients and families experience active engagement directed at ongoing QI, they feel attended to—even if some problems do not have an immediate solution. Sometimes answers to questions are less important than the patient’s and family’s perception that caregivers took the time to listen attentively.41

QUALITY IN CARE DELIVERY: A GOOD HABIT

NPMPs can play an active leadership role in QI in their organization. NPMPs are critical decision makers at the bedside, but they may also be called upon to share the helm with administrators and quality professionals working on the big picture of a practice or organization’s care delivery processes.31,42 NPMPs must make sure they seek a place at the table where decisions are being made, as they have the insight and training to effect meaningful changes in patient care. As lifelong learners, NPMPs have opportunities to develop skills to participate in QI and organizational change that enhance patients’ clinical outcomes and improve that which is more subjective but equally important: patient satisfaction. NPMPs can place themselves and their organizations on the map by identifying suboptimal aspects of care with regard to the three quality aspects discussed above (Figure 1).

Aristotle is credited as the first to say, “Excellence is not an act, but a habit.” Repeated acts create habit. In their repeated patient encounters, NPMPs have an enormous opportunity to think critically about actions they can take personally and changes that can be made within their health care organizations to optimize delivery of care to patients. NPMPs’ appreciation of the bedside process of care may give them insights into analysis and corrective actions that less-clinically intimate administrators may lack. Health care administrators and physician leaders are encouraged to harness the skills and experience of NPMPs, who can act as agents of change for health care QI and patient safety.4

Figure 1. Expanded role in three aspects of quality for nonphysician medical providers

NPMP = nonphysician medical provider.

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Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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References

Physicians, it is said, make the worst patients. Indeed, I have been accused of acting like the Black Knight in the movie *Monty Python and Holy Grail*, who after having his left arm defily removed by King Arthur’s sword examines his stump and proclaims, “Tis but a scratch!”

**A COUGHING MAN**

Last year an upper respiratory tract illness swept through our household, hitting first my youngest son, then his older brother, and finally me. Only my wife was spared. We coughed for days and days. Still, we trudged on, my sons going off to school and I to work in the hospital. My wife, the only one in our family not burdened with a Y chromosome, looked at us one night at the dinner table and exclaimed, “You know, you all probably have whooping cough.” What, I thought? We’ve all been vaccinated. It’s not possible. “Tis but a cough.

All three of us had our nasal passages probed the following day. The results were as expected—meaning my wife (an Alpha Omega Alpha graduate of the University of Illinois School of Medicine) was right. I left work with a bottle of antibiotics in hand and the hope of a speedy recovery. What was in store for me, however, was so much more.

My cough slowly began to improve, but the three-week illness had, unbeknownst to me, taken a toll on my vocal cords. A week after I finished the antibiotics I went to bed one night with my health seemingly on the mend. A few hours into a deep sleep, suddenly, something woke me up. I remember being awakened by some sort of sensation, but for the first several seconds I had no idea what had disturbed my sleep. Then, it hit me—I couldn’t breathe. I tried to breathe in. Nothing happened. I sat up and tried again. No air movement at all. I was, at this point, wide awake, and this new sensation had my full attention. I remember thinking to myself, “This isn’t a good thing.”

It’s not a common practice for me to suddenly sit bolt upright in the bed in the middle of the night, and my deviation from the norm awakened my wife. Just as she sat up, I was able to get a small amount of air in my lungs, accompanied by a brief song of stridor. I stood up and began to slowly walk to the bathroom. I don’t know why I went into the bathroom, but it just seemed like, if there was going to be some sort of medical drama, it should occur where there is white tile and bright lights. My wife, astutely, informed me she was going to call 911. “No,” I signalled with my hands, “I’ll be okay.” I just needed to breathe. In what my wife later described as the longest three minutes of her life, I slowly began to get control of my breathing, and within about five minutes I was breathing normally. “See,” I told her, “I was fine.”

I had experienced sleep-related laryngospasm, as I learned from reading about my symptoms the next day. It was probably brought on by my all my coughing and exacerbated by nocturnal gastroesophageal reflux. I assumed (because I have a Y chromosome) that it wouldn’t happen again, but I was wrong. My wife, at that point, very kindly referred me to one of my medical group’s otolaryngologists. I know that because I received a call from him that day, and he said, “Your wife told me I needed to see you.” A proper medical plan was then put in place to decrease nocturnal gastroesophageal reflux and to decrease nocturnal laryngospasms. Over the next month, I had only a couple of episodes of nocturnal laryngospasm, and I have been symptom free (off all treatment, as you might suspect from a compliant patient such as I) for the last eight months.

**A LAUGHING MAN**

You might think I’ve learned nothing (I still, after all, have a Y chromosome) from my experience, but you’d be wrong. Four months ago while in New Zealand, a patient was referred to me because of syncope. He was a 43-year-old farmer (Mr XY) who had seen his GP (general practitioner), at the insistence of his wife because of syncope (it seems a Y chromosome is equally disadvantageous across the Pacific Ocean, just as having two X chromosomes seems to add some sort of common sense to life). His GP noted the patient had recurrent episodes of syncope during bouts of laughter and referred the patient to me for internal medicine consultation. I read the referral and wondered if the patient might have laughter-induced, or gelastic, syncope.

First described in 1997 in a patient who experienced syncopen during laughter while watching the television show *Seinfeld*, and this was originally termed Seinfeld syncope. Since then a number of other reports of laughter-induced syncope have surfaced, with etiologies ranging from benign causes (vasovagal syncope) to more serious (a cerebellar tumor). Mr XY arrived at my office accompanied, and wisely so, by his wife. He had no significant past medical problems. His descriptions of the events which led to syncope were quite striking. The typical scenario was as follows: he would have a
normal day and be at the pub later in the evening where he would have eaten a substantial meal and consumed several glasses of beer. After dinner, he would be talking with his friends and invariably the conversations would induce copious amounts of laughter. Sometimes, he said, after a bout of laughter he would feel a tightening in his throat and then it would be difficult to get air into his lungs. At times, if he relaxed and concentrated on his breathing the feeling would go away in a few seconds, but at other times the sensation would progress to the point where, literally, he couldn't get any air into his lungs. This was followed shortly thereafter by him passing out. He would awaken on the floor anywhere from 10 to 20 seconds later and be able to breathe just fine. He did not have any chest pain, headaches (unless he had hit his head on the way down, which he rarely did) loss of bowel or bladder control, or seizure activity.

Mr XY described these episodes so well I immediately recognized he was describing laryngospasm. It was easy for me to recognize, of course, because I had experienced the same sensation. Laryngospasm is often precipitated by gastroesophageal reflux disease and is a well-documented cause of syncope.1 I surmised Mr XY’s large meal and several glasses of beer were contributors to the gastroesophageal reflux, and that his bouts of laughter likely increased the reflux, thus leading to laryngospasm. We discussed dietary and behavior changes to decrease gastroesophageal reflux, and he was prescribed omeprazole. In the 6 months since this intervention, he has had no further episodes of syncope.

A PATIENT’S STORY

There are enumerable ways to learn about diseases. Indeed, I have often commented on teaching rounds in the hospital that one way to accumulate knowledge of diseases would be to personally have every single disease known to man, and then it would be seemingly easy to recognize the symptoms in someone else. “Oh,” you might say to a patient, “you’re describing bitemporal hemianopsia. Yes, I had that in Autumn of 1997 when I was diagnosed with a pituitary tumor.” It would be a Herculean feat, however, to have all those diseases, and the number of physicians willing to participate in the plan might be few. Barring having every single disease known to man, an individual physician is left to his/her own medical experiences, the medical experiences of his/her family, and very poignantly, the experiences of his/her patients. And that, I believe, is the teaching point. If we listen carefully to our patients’ stories, they will tell us what we need to know. I’ll just check with my wife to see if I’m right.

References

Learning From Experience

Not even a dog-killer can learn his trade from books, but only from experience. And how much more is this true of the physician! … The art of medicine cannot be inherited, nor can it be copied from books.

— Selected Writings, Paracelsus, 1483-1541, Swiss German Renaissance physician, botanist, alchemist, astrologer, and general occultist; founder of the discipline of toxicology.
The 12-lead electrocardiogram has been referred to as an "11-lead study" on the basis of the false assumption that lead aVR yields only limited information. As this area is already covered by other leads (I, aVL, V\textsubscript{5}, V\textsubscript{6}), aVR was only used to confirm correct arm lead placement and was assumed to reflect only reciprocal changes from the lateral portion of the heart. As a result, the unpaired lead aVR has been largely ignored and has been coined the "forgotten lead."\textsuperscript{1} In reality, aVR is an informative lead that also reflects the right ventricular outflow tract and the basal portion of the interventricular septum. Analysis of aVR's individual waveforms should be performed in concert with all other leads because it can provide critical information in the management of a number of medical conditions.

The ST segment in lead aVR is used in the assessment of narrow complex tachyarrhythmia. Ho et al\textsuperscript{2} reported the presence of ST elevation in aVR has a 71% sensitivity and a 70% specificity of distinguishing atrial ventricular reciprocating tachycardia (such as Wolff-Parkinson-White) from atrial ventricular nodal reentrant tachycardia. In addition, aVR morphology can also be used to distinguish wide complex supraventricular tachycardia from ventricular tachycardia. For example, in 2008 Vereckei et al\textsuperscript{3} reported a 98% sensitivity in differentiating wide complex supraventricular tachycardia from ventricular tachycardia based solely on the analysis of aVR morphology (Figure 1).

The presence of a prominent R wave in aVR is a critical finding in sodium channel blocker poisonings, such as with tricyclic antidepressants.\textsuperscript{4} Liebelt et al\textsuperscript{5} concluded that an R wave amplitude > 3.0 mm is more sensitive than QRS interval as a predictor of seizures and ventricular dysrhythmias (Figure 2).

Finally, aVR is a valuable lead in the management of acute coronary ischemia. Although aVR ST-segment elevation may be an abnormal variant in supraventricular tachycardia, bundle branch blocks, left ventricular hypertrophy, or right ventricular hypertrophy, in the presence of other ischemic changes aVR ST-segment elevation is a sensitive indicator of left main, left anterior descending, or triple vessel disease.\textsuperscript{1-9} Barrabès et al\textsuperscript{10} and Kosuge et al\textsuperscript{11} have reported aVR ST-segment elevation to be an independent risk factor for increased morbidity and mortality. Therefore, the presence of aVR ST-segment elevation, in conjunction with other ischemic changes, should be considered an ST-segment elevation myocardial infarction equivalent and warrants immediate interventional reperfusion.\textsuperscript{6,7,10} (Figure 3).

Disclosure Statement
The author(s) have no conflicts of interest to disclose.

References


Section A.

Article 1. (page 30) Upstream Discussion Provided in the Ambulatory Setting to Assist Patients with Chronic Kidney Disease Considering Dialysis

Interdisciplinary consultations in the ambulatory setting may:
- a. create an epiphany for treatment planning
- b. help clarify patients’ treatment goals and the possibilities of medicine
- c. increase patient satisfaction with dialysis

All patients responding to the oral questionnaire:
- a. stated they would not want dialysis
- b. believed they did not have all of their questions answered
- c. stated they had a clear plan after the consult

Section B.

Refering to the CME articles, how likely is it that you will implement this learning to improve your practice within the next 3 months?

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<th>Objective</th>
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<td>Integrate learned knowledge and increase competence/confidence to support improvement and change in specific practices, behaviors, and performance.</td>
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<td>Lead in further developing “Patient-Centered Care” activities by acquiring new skills and methods to overcome barriers, improve physician/patient relationships, better identify diagnosis and treatment of clinical conditions, as well as, efficiently stratify health needs of varying patient populations.</td>
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<td>Implement changes and apply updates in services and practice/policy guidelines, incorporate systems and quality improvements, and effectively utilize evidence-based medicine to produce better patient outcomes.</td>
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Subjective Knowledge Confidence Scale: 0 = I already did this, 1 = highly unlikely, 2 = unlikely, 3 = unsure, 4 = likely, 5 = highly likely

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