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TABLE OF CONTENTS

Volume 12 | Number 9 | September 2017

ORIGINAL RESEARCH

BRIEF REPORTS

CHOOSING WISELY®: THINGS WE DO FOR NO REASON

Continued >

CLINCIAL CARE CONUNDRUMS

REVIEW

PERSPECTIVES IN HOSPITAL MEDICINE

EDITORIALS

LETTERS TO THE EDITOR

A Randomized Controlled Trial of a CPR Decision Support Video for Patients Admitted to the General Medicine Service

Aimee M. Merino, MD PhD[1*], Ryan Greiner, MD[2], and Kristopher Hartwig, MD, MPhil[3]

[1]Department of Medicine, Internal Medicine Residency Program, University of Minnesota, Minneapolis, Minnesota; [2]Department of Medicine, Hospital Medicine Program, North Memorial Medical Center, Robbinsdale, Minnesota; [3]Medical Director, Hospice and Palliative Care, Minneapolis VA Medical Center, Minneapolis, Minnesota

BACKGROUND: Patient preferences regarding cardiopulmonary resuscitation (CPR) are important, especially during hospitalization when a patient's health is changing. Yet many patients are not adequately informed or involved in the decision-making process.

OBJECTIVES: We examined the effect of an informational video about CPR on hospitalized patients' code status choices.

DESIGN: This was a prospective, randomized trial conducted at the Minneapolis Veterans Affairs Health Care System in Minnesota.

PARTICIPANTS: We enrolled 119 patients, hospitalized on the general medicine service, and at least 65 years old. The majority were men (97%) with a mean age of 75.

INTERVENTION: A video described code status choices: full code (CPR and intubation if required), do not resuscitate (DNR), and do not resuscitate/do not intubate (DNR/DNI). Participants were randomized to watch the video (n = 59) or usual care (n = 60).

MEASUREMENTS: The primary outcome was participants' code status preferences. Secondary outcomes included a questionnaire designed to evaluate participants' trust in their healthcare team and knowledge and perceptions about CPR.

RESULTS: Participants who viewed the video were less likely to choose full code (37%) compared to participants in the usual care group (71%) and more likely to choose DNR/DNI (56% in the video group vs. 17% in the control group) ($P < 0.00001$). We did not see a difference in trust in their healthcare team or knowledge and perceptions about CPR as assessed by our questionnaire.

CONCLUSIONS: Hospitalized patients who watched a video about CPR and code status choices were less likely to choose full code and more likely to choose DNR/DNI. *Journal of Hospital Medicine* 2017;12:700-704. © 2017 Society of Hospital Medicine

Discussions about cardiopulmonary resuscitation (CPR) can be difficult due to their association with end of life. The Patient Self Determination Act (H.R.4449 — 101st Congress [1989-1990]) and institutional standards mandate collaboration between care providers and patients regarding goals of care in emergency situations such as cardiopulmonary arrest. The default option is to provide CPR, which may involve chest compressions, intubation, and/or defibrillation. Yet numerous studies show that a significant number of patients have no code preference documented in their medical chart, and even fewer report a conversation with their care provider about their wishes regarding CPR.[1-3] CPR is an invasive and potentially painful procedure with a higher chance of failure than success[4], and yet many patients report that their provider did not discuss with them the risks and benefits of resuscitation.[5,6] Further highlighting the importance of individual discussions about CPR preferences is the reality that factors such as age and disease burden further skew the likelihood of survival after cardiopulmonary arrest.[7]

Complicating the lack of appropriate provider and patient discussion of the risks and benefits of resuscitation are significant misunderstandings about CPR in the lay population. Patients routinely overestimate the likelihood of survival following CPR.[8,9] This may be partially due to the portrayal of CPR in the lay media as highly efficacious.[10] Other factors known to prevent effective provider-and-patient discussions about CPR preferences are providers' discomfort with the subject[11] and perceived time constraints.[12]

Informational videos have been developed to assist patients with decision making about CPR and have been shown to impact patients' choices in the setting of life-limiting diseases such as advanced cancer,[13-14] serious illness with a prognosis of less than 1 year,[15] and dementia.[16] While discussion of code status is vitally important in end-of-life planning for seriously ill individuals, delayed discussion of CPR preferences is associated with a significant increase in the number of invasive procedures performed at the end of life, increased length of stay in the hospital, and increased medical cost.[17] Despite clear evidence that earlier discussion of resuscitation options are valuable, no studies have examined the impact of a video about code status options in the general patient population.

Here we present our findings of a randomized trial in patients hospitalized on the general medicine wards who were

*Address for correspondence and reprint requests: Aimee Merino, MD, Department of Medicine; 401 East River Parkway, VCRC 1st floor Suite 131, Minneapolis, MN 55125; Telephone: 612-625-5454; merin008@umn.edu.

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65 years of age or older, regardless of illness severity or diagnosis. The video tool was a supplement for, rather than a replacement of, standard provider and patient communication about code preferences, and we compared patients who watched the video against controls who had standard discussions with their providers. Our video detailed the process of chest compressions and intubation during CPR and explained the differences between the code statuses: full code, do not resuscitate (DNR), and do not resuscitate/do not intubate (DNR/DNI). We found a significant difference between the 2 groups, with significantly more individuals in the video group choosing DNR/DNI. These findings suggest that video support tools may be a useful supplement to traditional provider discussions about code preferences in the general patient population.

METHODS

We enrolled patients from the general medicine wards at the Minneapolis VA Hospital from September 28, 2015 to October 23, 2015. Eligibility criteria included age 65 years or older, ability to provide informed consent, and ability to communicate in English. Study recruitment and data collection were performed by a study coordinator who was a house staff physician and had no role in the care of the participants. The medical charts of all general medicine patients were reviewed to determine if they met the age criteria. The physician of record for potential participants was contacted to assess if the patient was able to provide informed consent and communicate in English. Eligible patients were approached and informed consent was obtained from those who chose to participate in the study. After obtaining informed consent, patients were randomized using a random number generator to the intervention or usual-care arm of the study.

Those who were assigned to the intervention arm watched a 6-minute long video explaining the code-preference choices of full code, DNR, or DNR/DNI. Full code was described as possibly including CPR, intubation, and/or defibrillation depending on the clinical situation. Do not resuscitate was described as meaning no CPR or defibrillation but possible intubation in the case of respiratory failure. Do not resuscitate/do not intubate was explained as meaning no CPR, no defibrillation, and no intubation but rather permitting "natural death" to occur. The video showed a mock code with chest compressions, defibrillation, and intubation on a mannequin as well as palliative care specialists who discussed potential complications and survival rates of inhospital resuscitation.

The video was created at the University of Minnesota with the departments of palliative care and internal medicine (www.mmcgmeservices.org/codestat.html). After viewing the video, participants in the intervention arm filled out a questionnaire designed to assess their knowledge and beliefs about CPR and trust in their medical care providers. They were asked to circle their code preference. The participants' medical teams were made aware of the code preferences and were counseled to discuss code preferences further if it was different from their previously documented code preference.

TABLE. Demographics and Comorbidities of Participants in Control and Intervention Arms

	Control	Intervention
Demographics and Comorbidities	n = 60	n = 59
Age, mean (SD)	75.8 (8.6)	75.2 (7.7)
Male sex, n (%)	60 (100)	55 (93)
White race, n (%)	54 (90)	50 (85)
Diagnosis, n (%)		
Cancer	8 (13)	8 (14)
Pulmonary disease	19 (32)	16 (27)
Heart failure	20 (33)	20 (34)
Renal dialysis	3 (5)	2 (3)
Cirrhosis	5 (8)	2 (3)
Stroke	6 (10)	6 (10)
Multiple morbidities	16 (27)	14 (24)

NOTE: Abbreviations: n, number; SD, standard deviation.

Participants in the control arm were assigned to usual care. At the institution where this study occurred, a discussion about code preferences between the patient and their medical team is considered the standard of care. After informed consent was obtained, participants filled out the same questionnaire as the participants in the intervention arm. They were asked to circle their code status preference. If they chose to ask questions about resuscitation, these were answered, but the study coordinator did not volunteer information about resuscitation or intervene in the medical care of the participants in any way.

Data collection included demographic and medical information from the participants' charts for race, sex, age, and primary diagnosis for hospitalization (Table). We also collected data on the presence or absence of end-stage kidney disease; progressive pulmonary diseases including chronic obstructive pulmonary disease and interstitial lung disease; cirrhosis of the liver; chronic heart failure; or active cancer (defined as currently undergoing treatment or metastatic). In both study arms, the questionnaire included questions to assess patient trust in their medical team, beliefs about resuscitation, and desire to continue life-prolonging interventions in the absence of likely recovery to the point of being discharged from the hospital. Possible responses occurred on a continuum from "agree," "agree somewhat," "neither agree nor disagree," "disagree somewhat," and "disagree."

All participants' demographic characteristics and outcomes were described using proportions for categorical variables and means ± standard deviation for continuous variables. The primary outcome was participants' stated code preference (full code, DNR, or DNR/DNI). Secondary outcomes included comparison of trust in medical providers, resuscitation beliefs, and desire for life-prolonging interventions as obtained from the questionnaire.

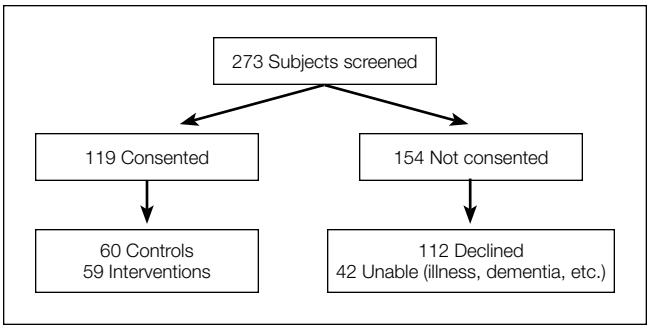

FIG. 1. A total of 273 patients were asked to participate. Of these, 119 patients enrolled. Of the 154 that did not enroll, 42 were either too ill or had mental status issues that precluded them from giving consent. A significant number of potential participants chose not to enroll, citing unwillingness to sign the consent paperwork, feeling too ill, or desiring more time to spend with visitors.

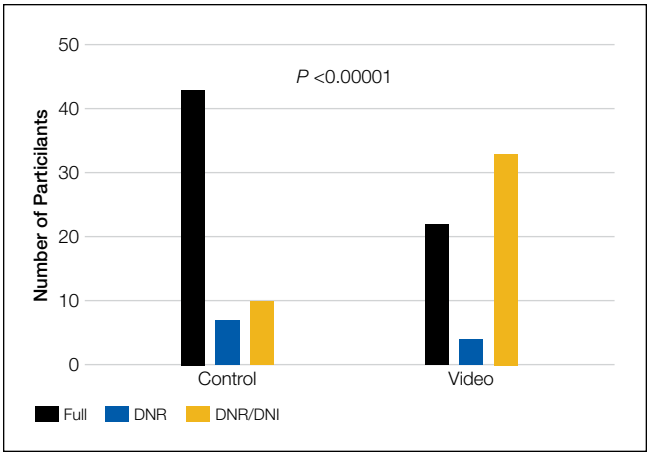

FIG. 2. Participants' code status choices in control and video arms.

NOTE: Abbreviations: DNR, do not resuscitate; DNR/DNI: do not resuscitate/do not intubate.

We analyzed code preferences between the intervention and control groups using Fisher exact test. We used analysis of variance (ANOVA) to compare questionnaire responses between the 2 groups. All reported *P* values are 2-sided with $P < 0.05$ considered significant. The project originally targeted a sample size of 194 participants for 80% power to detect a 20% difference in the code preference choices between intervention and control groups. Given the short time frame available to enroll participants, the target sample size was not reached. Propitiously, the effect size was greater than originally expected.

RESULTS

Study Participants

A total of 273 potentially eligible patients were approached to participate and 119 (44%) enrolled. (Figure 1). Of the 154 patients that were deemed eligible after initial screening, 42 patients were unable to give consent due to the severity of their illness or because of their mental status. Another 112 patients declined participation in the study, citing reasons such as disinterest in the consent paperwork, desire to spend time with visitors, and unease with the subject matter. Patients who declined participation did not differ significantly by age, sex, or race from those enrolled in the study.

Among the 119 participants, 60 were randomized to the control arm, and 59 were randomized to the intervention arm. Participants in the 2 arms did not differ significantly in age, sex, or race ($P > 0.05$), although all 4 women in the study were randomized to the intervention arm. Eighty-seven percent of the study population identified as white with the remainder including black, Asian, Pacific Islander, Native American, or declining to answer. The mean age was 75.8 years in the control arm vs. 75.2 years in the intervention arm.

Primary diagnoses in the study group ranged widely from relatively minor skin infections to acute pancreatitis. The control arm and the intervention arm did not differ significantly in the incidence of heart failure, pulmonary disease, renal dialysis, cirrhosis, stroke, or active cancer ($P > 0.05$). Patients were considered as having a stroke if they had suffered a stroke during their hospital admission or if they had long-term sequelae of prior stroke. Patients were considered as having active cancer if they were currently undergoing treatment or had metastases. Participants were considered as having multiple morbidities if they possessed 2 or more of the listed conditions. Between the control arm and the intervention arm, there was no significant difference in the number of participants with multiple morbidities (27% in the control group and 24% in the video group).

Code Status Preference

There was a significant difference in the code status preferences of the intervention arm and the control arm ($P < 0.00001$; Figure 2). In the control arm, 71% of participants chose full code, 12% chose DNR, and 17% chose DNR/DNI. In the intervention arm, only 37% chose full code, 7% chose DNR, and 56% chose DNR/DNI.

Secondary outcomes

Participants in the control and intervention arms were asked about their trust in their medical team (Question 1, Figure 3). There was no significant difference, but a trend towards less trust in the intervention group ($P = 0.083$) was seen with 93% of the control arm and 76% of the intervention arm agreeing with the statement "My doctors and healthcare team want what is best for me."

Question 2, "If I choose to avoid resuscitation efforts, I will not receive care," was designed to assess participants' knowledge and perception about the care they would receive if they chose DNR/DNI as their code status. No significant difference was seen between the control and the interventions arms, with 28% of the control group agreeing with the statement, compared to 22% of the video group.

For question 3, participants were asked to respond to the statement "I would like to live as long as possible, even if I never leave the hospital." No significant differences were seen between the control and the intervention arms, with 22% of both groups agreeing with the statement.

When we examined participant responses by the code status chosen, a significantly higher percentage of participants who chose full code agreed with the statement in question 3 ($P = 0.0133$). Of participants who chose full code, 27% agreed with the statement, compared to 18% of participants who chose DNR and 12% of participants who chose DNR/DNI. There was no significant difference ($P > 0.05$) between participant code status choice and either Question 1 or 2.

DISCUSSION

This study examined the effect of watching a video about CPR and intubation on the code status preferences of hospitalized patients. Participants who viewed a video about CPR and intubation were more likely to choose to forgo these treatments. Participants who chose CPR and intubation were more likely to agree that they would want to live as long as possible even if that time were spent in a medical setting.

To our knowledge, this is the first study to examine the role of a video decision support tool about code choices in the general hospital population, regardless of prognosis. Previous work has trialed the use of video support tools in hospitalized patients with a prognosis of less than 1 year,[15] patients admitted to the ICU,[18] and outpatients with cancer[18] and those with dementia.[16] Unlike previous studies, our study included a variety of illness severity.

Discussions about resuscitation are important for all adults admitted to the hospital because of the unpredictable nature of illness and the importance of providing high-quality care at the end of life. A recent study indicates that in-hospital cardiopulmonary arrest occurs in almost 1 per 1000 hospital days.[19] These discussions are particularly salient for patients 65 years and older because of the higher incidence of death in this group. Inpatient admission is often a result of a change in health status, making it an important time for patients to reassess their resuscitation preferences based on their physical state and known comorbidities.

Video tools supplement the traditional code status discussion in several key ways. They provide a visual simulation of the procedures that occur during a typical resuscitation. These tools can help patients understand what CPR and intubation entail and transmit information that might be missed in verbal discussions. Visual media is now a common way for patients to obtain medical information[20-22] and may be particularly helpful to patients who have low health literacy.[23]

Video tools also help ensure that patients receive all the facts about resuscitation irrespective of how busy their provider may be or how comfortable the provider is with the topic. Lastly, video tools can reinforce information that is shared in the initial code status discussion. Given the significant differences in code status preference between our control and video arms, it is clear that the video tool has a significant impact on patient choices.

While we feel that our study clearly indicates the utility of video tools in code status discussion in hospitalized patients, there are some limitations. The current study enrolled participants who were predominantly white and male. All participants were recruited from the Minneapolis Veterans Affairs Health Care System, Minnesota. The relatively homogenous study population may impact the study's generalizability. Another potential limitation of our study was the large number of

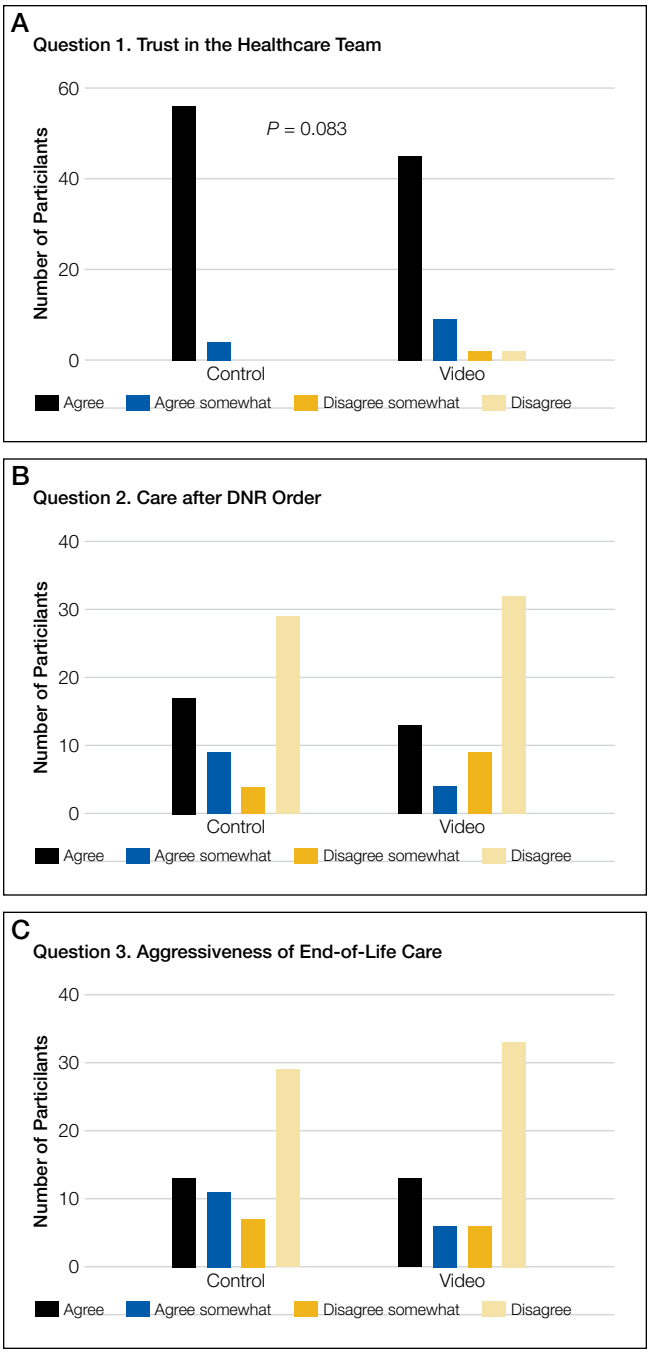

FIG. 3A-3C. Assessment of participant knowledge and beliefs about CPR in control and video arms. (A) Participants responded to the statement, "My doctors and healthcare team want what is best for me." (B) Participants responded to the statement, "If I choose to avoid resuscitation efforts, I will not receive care." (C) Participants responded to the statement, "I would like to live as long as possible, even if I never leave the hospital."

NOTE: Abbreviations: DNR, do not resuscitate.

eligible participants who declined to participate (41%), with many citing that they did not want to sign the consent paperwork. Additionally, the study coordinator was not blinded to the randomization of the participants, which could result in ascertainment bias. Also of concern was a trend, albeit non-significant, towards less trust in the healthcare team in the video group. Because the study was not designed to assess trust in the healthcare team both before and after the intervention, it is unclear if this difference was a result of the video.

Another area of potential concern is that visual images can be edited to sway viewers' opinions based on the way content is presented. In our video, we included input from palliative care and internal medicine specialists. Cardiopulmonary resuscitation and intubation were performed on a CPR mannequin. The risks and benefits of CPR and intubation were discussed, as were the implications of choosing DNR or DNR/DNI code statuses.

The questionnaire that we used to assess participants' knowledge and beliefs about resuscitation showed no differences between the control and the intervention arms of the study. We were surprised that a significant number of participants in the intervention group agreed with the statement, "If I choose to avoid resuscitation efforts, I will not receive care." Our video specifically addressed the common belief that choosing DNR/DNI or DNR code statuses means that a patient will not continue to receive medical care. It is possible that participants were confused by the way the question was worded or that they understood the question to apply only to care received after a cardiopulmonary arrest had occurred.

This study and several others[14-16] show that the use of video tools impacts participants' code status preferences. There is clinical and humanistic importance in helping patients make informed decisions regarding whether or not they would want CPR and/or intubation if their heart were to stop or if they were to stop breathing. The data suggest that video tools are an efficient way to improve patient care and should be made widely available.

Disclosures: The authors report no conflicts of interest.

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Patterns and Appropriateness of Thrombophilia Testing in an Academic Medical Center

Nicholas Cox, PharmD[1]*, Stacy A. Johnson, MD[1,2], Sara Vazquez, PharmD[1], Ryan P. Fleming, PharmD, BCPS[1], Matthew T. Rondina, MD[1-4], David Kaplan, MD[1,2], Stephanie Chauv, PharmD[5], Gabriel V. Fontaine, PharmD[5], Scott M. Stevens, MD[2,5], Scott Woller, MD[2,5], Daniel M. Witt, PharmD, BCPS, FCCP[1,6]

[1]University of Utah Health Care, Salt Lake City, Utah; [2]Department of Medicine, University of Utah School of Medicine, Salt Lake City, Utah; [3]GRECC, George E. Wahlen VAMC, Salt Lake City, Utah; [4]Molecular Medicine Program, University of Utah, Salt Lake City, Utah; [5]Intermountain Healthcare, Salt Lake City, Utah; [6]Department of Pharmacotherapy, University of Utah College of Pharmacy, Salt Lake City, Utah.

BACKGROUND: Clinical guidelines recommend against routine use of thrombophilia testing in patients with acute thromboembolism. Thrombophilia testing rarely changes acute management of a thrombotic event.

OBJECTIVE: To determine appropriateness of thrombophilia testing in a teaching hospital.

DESIGN: Retrospective cohort study.

SETTING: One academic medical center in Utah.

PARTICIPANTS: All patients who received thrombophilia testing between July 1, 2014, and December 31, 2014.

MAIN MEASUREMENTS: Proportion of thrombophilia tests occurring in situations associated with minimal clinical utility, defined as tests meeting at least 1 of the following criteria: discharged before results available; test type not recommended; testing in situations associated with decreased accuracy; duplicate testing; and testing following a provoked thrombotic event.

RESULTS: Overall, 163 patients received a total of 1451 thrombophilia tests for stroke (50% of tests; 35% of patients), venous thromboembolism (21% of tests; 21% of patients), and pregnancy-related conditions (15% of tests; 25% of patients). Of the 39 different test types performed, the most common were cardiolipin IgG and IgM antibodies (9% each), lupus anticoagulant (9%), and β_2-glycoprotein 1 IgG and IgM antibodies (8% each). In total, 911 tests (63%) were performed in situations associated with minimal clinical utility, with 126 patients (77%) receiving at least one such test. Only 2 patients (1%) had clear documentation of being offered genetic consultation.

CONCLUSIONS: Thrombophilia testing in this single-center study was often associated with minimal clinical utility. Strategies to improve testing practices (eg, hematology specialty consult prior to inpatient testing, improved order panels) might help minimize inappropriate testing and promote value-driven care. *Journal of Hospital Medicine* 2017;12:705-709. © 2017 Society of Hospital Medicine

Thrombophilia is a prothrombotic state, either acquired or inherited, leading to a thrombotic predisposition.[1] The most common heritable thrombophilias include factor V Leiden (FVL) and prothrombin G20210A. The most common acquired thrombophilia is the presence of phospholipid antibodies.[1] Thrombotic risk varies with thrombophilia type. For example, deficiencies of antithrombin, protein C and protein S, and the presence of phospholipid antibodies, confer higher risk than FVL and prothrombin G20210A.[2-5] Other thrombophilias (eg, methylenetetrahydrofolate reductase mutation, increased factor VIII activity) are relatively uncommon and/or their impact on thrombosis risk appears to be either minimal or unknown.[1-6] There is little clinical evidence that testing for thrombophilia impacts subsequent thrombosis prevention.[5,7,8] Multiple clinical guidelines and medical societies recommend against the routine and indiscriminate use of thrombophilia testing.[8-13] In general, thrombophilia testing should be considered only if the result would lead to changes in anticoagulant initiation, intensity, and/or duration, or might inform interventions to prevent thrombosis in asymptomatic family members.[8-13] However, thrombophilia testing rarely changes the acute management of a thrombotic event and may have harmful effects on patients and their family members because positive results may unnecessarily increase anxiety and negative results may provide false reassurance.[6,14-18] The cost-effectiveness of thrombophilia testing is unknown. Economic models have sought to quantify cost-effectiveness, but conclusions from these studies are limited.[7]

The utility of thrombophilia testing in emergency department (ED) and inpatient settings is further limited because patients are often treated and discharged before thrombophilia test results are available. Additionally, in these settings, multiple factors increase the risk of false-positive or false-negative results (eg, acute thrombosis, acute illness, pregnancy, and anticoagulant therapy).[19,20] The purpose of this study was to systematically assess thrombophilia testing

***Address for correspondence and reprint requests:** Nicholas Cox, PharmD, Department of Pharmacy Services, University of Utah Health Care, 50 N. Medical Drive, A-090M, Salt Lake City, UT 84132; Telephone: 435-650-5129; Fax: 801-585-0405; E-mail: nicholas.cox@pharm.utah.edu

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TABLE 1. Patient Characteristics

Characteristic	Patients n = 163
Age, mean (SD)	42 (15)
Female, n (%)	116 (71)
Race/ethnicity, n (%)	
White	131 (80)
Hispanic	14 (9)
Other	18 (11)
Native American, Alaskan, or other Pacific Islander	8 (5)
Asian	4 (2)
Unknown	6 (4)
Black or African American	3 (2)
Patient location, n (%)	
Inpatient	157 (96)
Emergency department	6 (4)
Length of stay in days, mean (SD)	9 (13)
Acute thrombosis identified during admission, n (%)	43 (26)
Prior thrombosis history, n (%)	34 (21)
Prior stroke history, n (%)	18 (11)

NOTE: Abbreviation: SD, standard deviation.

TABLE 2. Thrombophilia Testing Characteristics

Characteristic	Tests n = 1451
Tests by hospital service, n (%)	
Neurology	597 (41)
Internal Medicine	293 (20)
Obstetrics and Gynecology	227 (16)
Neurosurgery	151 (11)
General Surgery	139 (10)
Physical Medicine and Rehabilitation	23 (2)
Psychiatry	11 (1)
Family/Preventative Medicine	5 (<1)
Orthopedic Surgery	5 (<1)
Tests per patient, mean (SD)	8.9 (6.0)
Tests ordered as part of a panel of tests, n (%)[a]	1150 (79)
Days from admission to time test ordered, mean (SD)	2.7 (5.7)

[a] See Supplementary Table 5 for tests included in each panel.

NOTE: Abbreviation: SD, standard deviation.

TABLE 3. Indications for Thrombophilia Testing

Indication[a]	Tests, n (%) n = 1451	Patients, n (%) n = 163
Ischemic stroke	726 (50)	57 (35)
Cryptogenic or other etiology	498 (34)	40 (25)
Cerebral venous sinus thrombosis[b]	154 (11)	11 (7)
Basilar artery thrombosis	41 (3)	2 (1)
Cardioembolic origin	33 (2)	4 (2)
Venous thromboembolism	298 (21)	35 (21)
Deep vein thrombosis	147 (10)	16 (10)
Pulmonary embolism	103 (7)	13 (8)
Other[c]	54 (4)	7 (4)
Pregnancy related[d]	215 (15)	41 (25)
Nonstroke arterial thrombosis[e]	49 (3)	5 (3)
History of thrombophilia[f]	44 (3)	10 (6)
Unclear	13 (1)	4 (2)
Other[g]	219 (15)	27 (17)

[a] Indications are not mutually exclusive. Testing may have been prompted by multiple factors (eg, stroke + VTE).

[b] Cerebral venous sinus thrombosis categorized based on presenting symptoms, rather than underlying pathophysiology.

[c] Other venous thromboembolism indications include superficial vein thrombosis, portal vein thrombosis, superior mesenteric vein thrombosis, and others.

[d] Pregnancy-related conditions include preeclampsia, intrauterine fetal demise, intrauterine growth restriction, decreased fetal movements, history of miscarriages, and others.

[e] Nonstroke arterial thrombosis indications include extremity thrombosis, acute coronary syndrome, and others.

[f] Defined as tests ordered to validate patient-reported thrombophilia conditions.

[g] Other indications include systemic lupus erythematosus, thrombotic microangiopathy, cerebral amyloid angiopathy, catastrophic antiphospholipid syndrome, hemolytic anemia, supratherapeutic INR in a patient not on anticoagulant therapy, and a bleeding event while taking long-term anticoagulant therapy.

NOTE: Abbreviations: INR, international normalized ratio; VTE, venous thromboembolism.

patterns in the ED and hospitalized patients at an academic medical center and to quantify the proportion of tests associated with minimal clinical utility. We hypothesize that the majority of thrombophilia tests completed in the inpatient setting are associated with minimal clinical utility.

METHODS

Setting and Patients

This study was conducted at University of Utah Health Care (UUHC) University Hospital, a 488-bed academic medical center with a level I trauma center, primary stroke center, and 50-bed ED. Laboratory services for UUHC, including thrombophilia testing, are provided by a national reference laboratory, Associated Regional and University Pathologists Laboratories. This study included patients ≥18 years of age who received thrombophilia testing (Supplementary Table 1) during an ED visit or inpatient admission at University Hospital between July 1, 2014 and December 31, 2014. There were no exclusion criteria. An institutional electronic data repository was used to identify patients matching inclusion criteria. All study activities were reviewed and approved by the UUHC Institutional Review Board with a waiver of informed consent.

Outcomes

An electronic database query was used to identify patients, collect patient demographic information, and collect test characteristics. Each patient's electronic medical record was manually reviewed to collect all other outcomes. Indication for thrombophilia testing was identified by manual review of provider notes. Thrombophilia tests occurring in situations associated with minimal clinical utility were defined as tests meeting at least one of the following criteria: pa-

TABLE 4. Clinical Utility of Thrombophilia Testing

Characteristic	Tests, n (%) n = 1451	Patients, n (%) n = 163
Tests occurring in situations associated with minimal clinical utility	911 (63)[a]	126 (77)[a]
Test type not recommended by guidelines or by University of Utah Health Care Thrombosis Service physicians	417 (29)	71 (44)
Discharged before test results available	381 (26)	65 (40)
Receiving anticoagulant therapy at time of test[b]	230 (16)	71 (44)
Acute thrombosis at time of test[b]	218 (15)	40 (25)
Provoked thrombotic events[c]	137 (9)	12 (7)
Thrombosis occurred while pregnant, <8 weeks postpartum, or while on estrogen-containing medications	119 (8)	8 (5)
Thrombosis occurred within 3 months following major surgery	18 (1)	4 (2)
Duplicate testing	41 (3)	14 (9)
Pregnant, <8 weeks postpartum, or on estrogen-containing medications at time of test[b]	29 (2)	11 (7)

[a] Total represents the number of tests or patients meeting one of the characteristics listed in the table. Characteristics are not mutually exclusive.

[b] Analysis includes only test types whose accuracy is known to be affected by the respective characteristic. See Supplementary Table 3 for tests included in the analysis of each characteristic.

[c] Analysis includes only tests for which the indication for thrombophilia testing was an acute thrombosis.

tient discharged before test results were available for review; test type not recommended by published guidelines or by UUHC Thrombosis Service physicians for thrombophilia testing (Supplementary Table 2); test performed in situations associated with decreased accuracy; test was a duplicate test as a result of different thrombophilia panels containing identical tests; and test followed a provoked venous thromboembolism (VTE). Testing in situations associated with decreased accuracy are summarized in Supplementary Table 3 and included at least one of the following at the time of the test: anticoagulant therapy, acute thrombosis, pregnant or <8 weeks postpartum, and receiving estrogen-containing medications. Only test types known to be affected by the respective situation were included. Testing following a provoked VTE was defined as testing prompted by an acute thrombosis and performed within 3 months following major surgery (defined administratively as any surgery performed in an operating room), during pregnancy, <8 weeks postpartum, or while on estrogen-containing medications. Thrombophilia testing during anticoagulant therapy was defined as testing within 4 half-lives of anticoagulant administration based on medication administration records. Anticoagulant therapy changes were identified by comparing prior-to-admission and discharge medication lists.

Data Analysis

Patient and laboratory characteristics were summarized using descriptive statistics, including mean and standard deviation (SD) for continuous variables and proportions for categorical variables. Data analysis was performed using Excel (Version 2013, Microsoft Corporation. Redmond, Washington).

RESULTS

During the 6-month study period, 163 patients received at least 1 thrombophilia test during an ED visit or inpatient admission. Patient characteristics are summarized in Table 1. Tested patients were most commonly inpatients (96%) and female (71%). A total of 1451 thrombophilia tests were performed with a mean (± SD) of 8.9 ± 6.0 tests per patient. Testing characteristics are summarized in Table 2. Of the 39 different test types performed, the most commonly ordered were cardiolipin IgG and IgM antibodies (9% each), lupus anticoagulant (9%), and β_2-glycoprotein 1 IgG and IgM antibodies (8% each). When combined with testing for phosphatidyl antibodies, antiphospholipid tests accounted for 70% of all tests. Overall, 134 (9%) test results were positive. The mean time for results to become available was 2.2 ± 2.5 days. The frequency of test types with corresponding positivity rates and mean time for results to become available are summarized in Supplementary Table 4.

The indications for thrombophilia testing are summarized in Table 3. Ischemic stroke was the most common indication for testing (50% of tests; 35% of patients), followed by VTE (21% of tests; 21% of patients), and pregnancy-related conditions (eg, preeclampsia, intrauterine fetal demise; 15% of tests; 25% of patients). Overall, 911 tests (63%) occurred in situations associated with minimal clinical utility, with 126 patients (77%) receiving at least one of these tests (Table 4).

Anticoagulant therapy was changed in 43 patients (26%) in the following ways: initiated in 35 patients (21%), transitioned to a different anticoagulant in 6 patients (4%), and discontinued in 2 patients (1%). Of the 35 patients initiating anticoagulant therapy, 29 had documented thrombosis (24 had VTE, 4 had cerebral venous sinus thrombosis [CVST], and 1 had basilar artery thrombosis). Overall, 2 instances were identified in which initiation of anticoagulant therapy at discharge was in response to thrombophilia test results. In the first instance, warfarin without a parenteral anticoagulant bridge was initiated for a 54-year-old patient with a cryptogenic stroke who tested positive for β_2-glycoprotein 1 IgG antibodies, lupus anticoagulant, and protein S deficiency. In the second instance, warfarin with an enoxaparin bridge was initiated for a 26-year-old patient with a cryptogenic stroke who tested positive for β_2-glycoprotein 1 IgG and IgM antibodies, cardiolipin IgG antibodies, lupus anticoagulant, protein C deficiency, and antithrombin deficiency. Of the 163 patients receiving thrombophilia testing, only 2 patients (1%) had clear documentation of being offered genetic consultation.

DISCUSSION

In this retrospective analysis, 1451 thrombophilia tests were performed in 163 patients over 6 months. Tested patients

were relatively young, which is likely explained by the number of patients tested for pregnancy-related conditions and the fact that a stroke or VTE in younger patients more frequently prompted providers to suspect thrombophilia. Nearly three-fourths of patients were female, which is likely due to testing for pregnancy-related conditions and possibly diagnostic suspicion bias given the comparative predilection of antiphospholipid syndrome for women. The patient characteristics in our study are consistent with other studies evaluating thrombophilia testing.[21,22]

Thrombophilia testing was most frequently prompted by stroke, VTE, and pregnancy-related conditions. Only 26% of patients had acute thrombosis identified during the admission, primarily because of the high proportion of tests for cryptogenic strokes and pregnancy-related conditions. Thrombophilia testing is recommended in patients who have had a stroke when the stroke is considered to be cryptogenic after a standard stroke evaluation.[23] Thrombophilia testing in pregnancy-related conditions is controversial but is often considered in situations such as stillbirths with severe placental pathology and/or significant growth restriction, or in mothers with a personal or family history of thrombosis.[24] The proportion of testing for pregnancy-related conditions may be greater than at other institutions because UUHC Maternal Fetal Medicine is a referral center for women with conditions associated with hypercoagulability. Anticoagulant therapy was initiated in 21% of patients, but specifically in response to thrombophilia testing in only 2 instances; in most cases, anticoagulant therapy was initiated regardless of thrombophilia test results.

The results of this study confirm our hypothesis because the majority of thrombophilia tests occurred in situations associated with minimal clinical utility. Testing in these situations was not isolated to specific patients or medical services because 77% of tested patients received at least 1 test associated with minimal clinical utility. Our study took a conservative approach in defining scenarios associated with minimal clinical utility because other situations can also affect testing accuracy (eg, hepatic disease, nephrotic syndrome) but were not included in our analysis of this outcome.

The results of this study highlight opportunities to improve thrombophilia testing practices at our institution and may be generalizable to institutions with similar testing patterns. Because multiple medical services order thrombophilia tests, strategies to improve testing practices are still being determined. The results of this study can serve as a baseline for comparison after strategies are implemented. The most common situation associated with minimal clinical utility was the use of test types not generally recommended by guidelines or UUHC Thrombosis Service physicians for thrombophilia testing (eg, β_2-glycoprotein 1 IgA antibodies, phosphatidyl antibodies). We intend to require a hematology or thrombosis specialty consult prior to ordering these tests. This intervention alone could potentially decrease unnecessary testing by a third. Another consideration is to require a specialty consult prior to any inpatient thrombophilia testing. This strategy has been found to decrease inappropriate testing at other institutions.[21] We also intend to streamline available thrombophilia testing panels because a poorly designed panel could lead to ordering of multiple tests associated with minimal clinical utility. At least 12 different thrombophilia panels are currently available in our computerized physician order entry system (see Supplementary Table 5). We hypothesize that current panel designs contribute to providers inadvertently ordering unintended or duplicate tests and that reducing the number of available panels and clearly delineating what tests are contained in each panel is likely to reduce unnecessary testing. Other strategies being considered include using electronic clinical decision support tools, implementing strict ordering criteria for all inpatient testing, and establishing a thrombosis stewardship program.

Our study was unique in at least 2 ways. First, previous studies describing thrombophilia testing have described testing patterns for patients with specific indications (eg, VTE), whereas our study described all thrombophilia tests regardless of indication. This allows for testing pattern comparisons across indications and medical services, increasing the generalizability of our results. Second, this study quantifies tests occurring in situations associated with a practical definition of minimal clinical utility.

Our study has several limitations: (1) Many variables were reliant on provider notes and other documentation, which allows for potential misclassification of variables. (2) It was not always possible to determine the ultimate utility of each test in clinical management decisions, and our study did not investigate the impact of thrombophilia testing on duration of anticoagulant therapy. Additionally, select situations could benefit from testing regardless if anticoagulant therapy is altered (eg, informing contraceptive choices). (3) Testing performed following a provoked acute thrombosis was defined as testing within 3 months following administratively defined major surgery. This definition could have included some minor procedures that do not substantially increase VTE risk, resulting in underestimated clinical utility. (4) The UUHC University Hospital serves as a referral hospital for a large geographical area, and investigators did not have access to outpatient records for a large proportion of discharged patients. As a result, frequency of repeat testing could not be assessed, possibly resulting in overestimated clinical utility. (5) In categorizing indications for testing, testing for CVST was subcategorized under testing for ischemic stroke based on presenting symptoms rather than on underlying pathophysiology. The rationale for this categorization is that patients with CVST were often tested based on presenting symptoms. Additionally, tests for CVST were ordered by the neurology service, which also ordered tests for all other ischemic stroke indications. (6) The purpose of our study was to investigate the subset of the hospital's patient population that received thrombophilia testing, and patients were identified by tests received and not by diagnosis codes. As a result, we are unable to provide the proportion of total patients treated at the hospital for specific condi-

tions who were tested (eg, the proportion of stroke patients that received thrombophilia testing). (7) Current practice guidelines do not recommend testing for phosphatidyl antibodies, even when traditional antiphospholipid testing is negative.[25-27] Although expert panels continue to explore associations between phosphatidyl antibodies and pregnancy morbidity and thrombotic events, the low level of evidence is insufficient to guide clinical management.[28] Therefore, we categorized all phosphatidyl testing as associated with minimal clinical utility.

CONCLUSIONS

In a large academic medical center, the majority of tests occurred in situations associated with minimal clinical utility. Strategies to improve thrombophilia testing practices are needed in order to minimize potentially inappropriate testing, provide more cost-effective care, and promote value-driven outcomes.

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Influenza Season Hospitalization Trends in Israel: A Multi-Year Comparative Analysis 2005/2006 Through 2012/2013

Aharona Glatman-Freedman, MD, MPH[1-3]*, Zalman Kaufman, MSc[1], Yaniv Stein, BSc[1], Hanna Sefty, MSc[1], Hila Zadka, PhD[1], Barak Gordon, MD, MHA[4], Jill Meron, BSc[5], Ethel-Sherry Gordon, PhD[5], Rita Dichtiar, BSc[1], Ziona Haklai, MSc[5], Arnon Afek, MD[3,6], Tamy Shohat, MD, MPH[1,3]

[1]The Israel Center for Disease Control, Ministry of Health, Tel Hashomer, Israel; [2]Departments of Pediatrics and Family and Community Medicine, New York Medical College, Valhalla, New York; [3]Department of Epidemiology and Preventive Medicine, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [4]Department of Family Medicine, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [5]Division of Health Information, Ministry of Health, Jerusalem, Israel; [6]Medical Administration, Ministry of Health, Jerusalem, Israel.

BACKGROUND: Influenza-related morbidity impacts healthcare systems, including hospitals.

OBJECTIVE: To obtain a quantitative assessment of hospitalization burden in pediatric and internal medicine departments during influenza seasons compared with the summer months in Israel.

METHODS: Data on pediatric and internal medicine hospitalized patients in general hospitals in Israel during the influenza seasons between 2005 and 2013 were analyzed for rate of hospitalizations, rate of hospitalization days, hospital length of stay (LOS), and bed occupancy and compared with the summer months. Data were analyzed for hospitalizations for all diagnoses, diagnoses of respiratory or cardiovascular disease (ICD9 390-519), and influenza or pneumonia (ICD9 480-487), with data stratified by age. The 2009-2010 pandemic influenza season was excluded.

RESULTS: Rates of monthly hospitalizations and hospitalization days for all diagnoses were 4.8% and 8% higher, respectively, during influenza seasons as compared with the summers. The mean LOS per hospitalization for all diagnoses demonstrated a small increase during influenza seasons as compared with summer seasons. The excess hospitalizations and hospitalization days were especially noticed for the age groups under 1 year, 1-4 years, and 85 years and older. The differences were severalfold higher for patients with a diagnosis of respiratory or cardiovascular disease and influenza or pneumonia. Bed occupancy was higher during influenza seasons compared with the summer, particularly in pediatric departments.

CONCLUSIONS: Hospital burden in pediatric and internal medicine departments during influenza seasons in Israel was associated with age and diagnosis. These results are important for optimal preparedness for influenza seasons. *Journal of Hospital Medicine* 2017;12:710-716. © 2017 Society of Hospital Medicine

Influenza-associated morbidity poses a significant hospital burden.[1] A study from the United States estimated that seasonal influenza is responsible for 3.1 million hospitalization days per year.[2]

Assessment of hospital burden during influenza seasons presents a challenge due to several possible factors, such as inaccurate recording of diagnosis[3] and incomplete age group data. Although great emphasis has historically been placed on older age groups, a study from England and Wales showed that the number of hospitalizations and deaths resulting from influenza was significantly higher in children as compared with adults.[4] Moreover, excess visits to emergency departments in New York City because of fever and respiratory morbidity during influenza seasons were found mostly among school-age children, whereas in adults, the surplus was small to nonexistent.[5]

***Address for correspondence and reprint requests:** Aharona Glatman-Freedman, MD, MPH, Israel Center for Disease Control, Gertner Institute, Sheba Medical Center, Tel Hashomer, 5265601, Israel; Telephone: 972-3-7371508; Fax: 972-2-5655994; E-mail: aharona.freedman@moh.health.gov.il

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Studies examining influenza-related hospitalizations evaluated numbers and rates of hospitalization.[6-11] However, information regarding length of hospitalizations, hospitalizations during the influenza season that were not influenza related, or comparisons between influenza seasons and summer seasons is scarce. These determinants are of great importance for hospital preparedness towards influenza seasons. The aim of the current study was to estimate excess hospitalizations and length of hospitalization during influenza seasons, as compared with the summer, in different age groups and selected diagnoses in Israel.

METHODS

Data Sources

Hospitalization data of internal medicine and pediatric departments in 28 acute care hospitals in Israel between 2005 and 2013 were obtained from the National Hospital Discharges Database managed by the Health Information Division (HID) in the Israel Ministry of Health (MOH). The information included number of discharges (including in-hospital deaths), number of hospitalization days, and the mean length of stay (LOS) per discharge for all diagnoses and for primary or secondary diagnoses of respiratory/cardiovascular disease (ICD9 390-519) and influenza/pneumonia (ICD9 480-487).

Bed occupancy rates for internal medicine and pediatric departments were based on the National Patient Flow Database managed by the HID.

The 2009-2010 pandemic influenza season was excluded from analysis due to different morbidity patterns and timing (April 2009 until August 2010) as compared with seasonal influenza.

Data Classification

Hospitalizations data were analyzed for all ages, for specific age groups (the first year of life [0], ages 1-4, 5-14, 15-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84, and 85 years and older), for all diagnoses, and for primary or secondary discharge diagnosis of respiratory/cardiovascular disease (ICD9 390-519) and influenza/pneumonia (ICD9 480-487).

Duration of Influenza Season

The beginning and the end of the influenza season were determined by the National Influenza surveillance program, which includes on average 22 community sentinel clinics, throughout Israel, each influenza season. These clinics send nose-throat samples from a convenience sample of patients with influenza-like illness (ILI), from week 40 of each year until the end of the influenza season in the subsequent year. These samples are analyzed for the presence of influenza virus by real-time reverse transcription polymerase chain reaction (RT-PCR) at the Central Virology Laboratory of Israel. Based on influenza virus detection in nose-throat samples from patients with ILI attending the community sentinel clinics, we determined the first and last month of each influenza season. The first month in which positive influenza samples were identified in sequence was defined as the first month of the season. The month in which the sequence of positive influenza samples stopped was defined as the last month of the season.

The 2009-2010 pandemic influenza season was excluded from analysis due to different morbidity patterns and timing (April 2009 until August 2010) as compared with seasonal influenza.

Data Analysis

Rates. Rates of monthly hospitalizations and monthly hospitalization days were calculated per 100,000 residents for all ages and for the specific age groups. Estimated average population sizes in different years for all ages and for specific age groups were obtained from the Central Bureau of Statistics (http://www.cbs.gov.il/reader/shnaton/templ_shnaton.html?num_tab=st02_01&CYear=2014). Monthly LOS was not converted to rates.

Hospitalizations. Mean monthly rate of hospitalizations during influenza and summer seasons was calculated by dividing the sum of hospital discharge rates during influenza/summer seasons of the entire evaluation period (2005/2006 to 2012/2013) by the number of influenza/summer activity months of that period.

Hospitalization Days. The measure "hospitalization days" refers to the hospitalization days of all patients who were discharged during influenza seasons. Mean monthly rate of hospitalization days during the influenza season and summer season was calculated using the procedure described for monthly mean rate of hospitalizations.

Length of Stay. The measure "length of stay" refers to the number of days that individual patients stayed in the hospital during an admission in the evaluated seasons.

Mean monthly LOS during the influenza and summer seasons for all patients (in both internal medicine and pediatric departments) and by age group was calculated by dividing the sum of monthly LOS during influenza seasons/summer season of the entire evaluation period (2005/2006 to 2012/2013 except for the 2009/2010 season) by the number of influenza/summer activity months of that period.

LOS for each specific month of the evaluation period for a single patient was calculated by dividing the number of hospitalization days of all patients that were discharged that month (stratified by age group) by the number of discharges in the same month.

Bed Occupancy. Bed occupancy rates for internal medicine and pediatric departments of the seasons evaluated were computed as a weighted rate based on the hospitalization days and licensed inpatient beds for the period of each influenza and summer season. The calculation took into account the number of days of each month and was based on the monthly reporting of hospital inpatient days in these departments and on the number of inpatient beds according to standard license documents issued by the MOH for each hospital.

Difference Between Influenza and Summer Seasons. Differences in mean monthly rates of hospitalizations, mean monthly rate of hospitalization days, and LOS during influenza seasons and the preceding summer were calculated as absolute numbers per month and as a percentage. The difference between bed occupancy during the influenza seasons and the preceding summers was expressed in percentage. Differences were computed for all diagnoses and for ICD9 480-487 and 390-519.

Statistical Analysis

Mean and standard deviation for monthly hospitalization rates, rates of monthly hospitalization days, and for LOS were calculated for all the influenza and summer seasons that were evaluated. Differences and statistical significance for these parameters were evaluated using a two-tailed Wilcoxon-Mann-Whitney test adjusted for ties, with 95% confidence interval for mean locations. The null hypothesis of the Wilcoxon test used was that the mean ranks of the influenza and summer season observations were equal.

Mean of bed occupancy percentage was calculated for influenza and summer seasons, with the difference and statistical significance being evaluated using a χ^2 test. P value of < 0.05 was considered statistically significant. SAS Version 9.1 and R program version 3.3.1 software were used for analysis.

RESULTS

Influenza Seasons

The length of influenza seasons varied, with the shortest season lasting 3 months (2006-2007) and the longest season last-

TABLE 1. Start and End Months of Influenza Seasons by Year

Season	Start	End
2005/2006	1/2006	4/2006
2006/2007	12/2006	2/2007
2007/2008	12/2007[b]	3/2008
2008/2009	12/2008	4/2009[b]
2009/2010	not included	not included
2010-2011	10/2010[a]	3/2011
2011/2012	11/2011[b]	4/2012[a]
2012/2013	12/2012	3/2013

[a] 3 weeks of influenza activity.
[b] 2 weeks of influenza activity.

ing six months (2010-2011 and 2011-2012; Table 1). Of the 14 first and last months of the 7 influenza seasons, 9 had influenza activity throughout the month, 2 had 3 weeks of influenza activity, and 3 had 2 weeks of influenza activity (Table 1).

Hospitalizations

A total of 452,209 hospital discharges occurred in pediatric and internal medicine departments during the influenza seasons that were evaluated. The mean monthly rate of hospitalizations (as defined in METHODS) for all patients was 4.8% higher during influenza seasons as compared with the preceding summer seasons (panel A in Figure; Supplementary Table 1). Analysis by age groups revealed a statistically significant increase during influenza seasons in the younger and older age groups (panel A in Figure; Supplementary Table 1). Specifically, the increase for all diagnoses was 32.8%, 16.7%, and 14.1% for infants <1 year, children aged 1-4 years, and adults ≥85 years, respectively (panel A in Figure; Supplementary Table 1).

The mean monthly rate of hospitalizations for all ages due to the diagnosis of respiratory/cardiovascular diseases and influenza/pneumonia was 18.6% and 60.8% higher, respectively, during influenza seasons compared with the preceding summers (panels B and C in Figure). These differences were statistically significant (panels B and C in Figure; Supplementary Table 1).

The increase in mean monthly hospitalization rates for patients with a diagnosis of respiratory/cardiovascular diseases and pneumonia/influenza was highest among infants <1 year and children aged 1-4 years (panels B and C in Figure; Supplementary Table 1). Increases were also observed among other age groups. However, they were more modest and reached statistical significance for respiratory/cardiovascular diseases in the age groups of ≤34 years and ≥75 years (panel B in Figure; Supplementary Table 1). The increases in mean monthly hospitalization rates for pneumonia/influenza were statistically significant in all age groups and were greater than 40% among adults ≥55 years (panel C in Figure; Supplementary Table 1).

Statistically significant decreases in mean monthly hospitalization rates during influenza seasons were observed for all

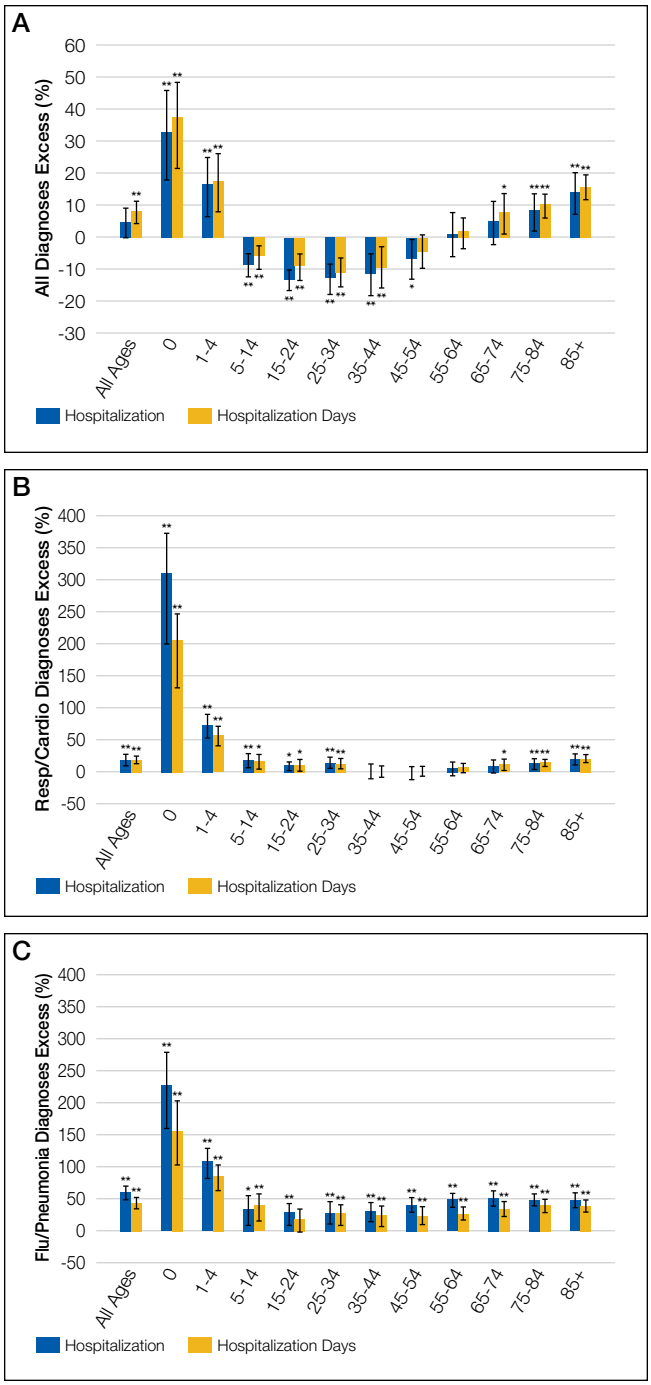

FIG. (A) Monthly mean excess hospitalization rates, and hospitalization days rates, during influenza seasons compared with the preceding summers, 2005-2013, for all diagnoses; (B) respiratory/cardiovascular diseases (ICD9 390-519); and (C) influenza/pneumonia (ICD9 480-487). NOTE: Y error bars represent 95% Confidence Interval (CI) for mean locations; * denotes *P* value < .05; ** denotes *P* value < .01.

TABLE 2. Mean Monthly Length of Stay per Discharge During Influenza Season Compared With the Preceding Summer, 2005-2013

Age (Years)	Diagnoses (ICD9 code)	Summer Mean (SD)	Influenza Mean (SD)	Absolute Difference Between Influenza and Preceding Summer Season (Days)	Difference Between Influenza and Preceding Summer Season (%)	Wilcoxon *P* Value
All	All	4.04 (0.12)	4.19 (0.17)	0.15	3.7	<.01
	Resp/Cardio (390-519)	4.71 (0.23)	4.73 (0.24)	0.02	0.3	.78
	Flu/Pneumo (480-487)	6.71 (0.41)	6.03 (0.41)	–0.68	–10.1	<.001
0	All	3.74 (0.20)	3.87 (0.22)	0.13	3.6	<.05
	Resp/Cardio (390-519)	5.96 (0.80)	4.58 (0.58)	–1.38	–23.1	<.001
	Flu/Pneumo (480-487)	6.03 (1.48)	4.78 (0.63)	–1.25	–20.7	<.01
1-4	All	3.10 (0.17)	3.12 (0.13)	0.02	0.5	.37
	Resp/Cardio (390-519)	3.92 (0.56)	3.54 (0.13)	–0.38	–9.6	<.01
	Flu/Pneumo (480-487)	4.03 (0.64)	3.56 (0.19)	–0.46	–11.5	<.01
5-14	All	3.21 (0.18)	3.32 (0.14)	0.11	3.3	<.01
	Resp/Cardio (390-519)	4.31 (0.51)	4.22 (0.38)	–0.09	–2.1	.52
	Flu/Pneumo (480-487)	4.49 (1.02)	4.60 (0.66)	0.12	2.6	.18
15-24	All	3.11 (0.18)	3.25 (0.20)	0.14	4.5	<.01
	Resp/Cardio (390-519)	4.2 (0.53)	4.22 (0.52)	0.02	0.6	.62
	Flu/Pneumo (480-487)	5.66 (1.32)	5.21 (1.29)	–0.45	–8.0	.43
25-34	All	3.21 (0.27)	3.28 (0.27)	0.08	2.3	.44
	Resp/Cardio (390-519)	4.06 (0.56)	4.02 (0.56)	–0.04	–0.9	.75
	Flu/Pneumo (480-487)	4.89 (1.11)	4.85 (1.10)	–0.04	–0.8	.94

Continued on page 713

diagnoses in the 5-54 age groups (panel A in Figure; Supplementary Table 1). Decreases were not seen for the diagnoses of respiratory/cardiovascular diseases or pneumonia/influenza (panels B and C in Figure; Supplementary Table 1).

Hospitalization Days

The mean monthly rate of hospitalization days per 100,000 residents showed a similar trend to that of the hospitalization rates (panels A, B, and C in Figure; Supplementary Table 2), with the most prominent increases observed among infants and children <5 years and adults ≥65 years.

The mean monthly rate of hospitalization days per 100,000 during influenza seasons for all ages due to all diagnoses was 8% higher ($P < 0.001$) as compared with the summer seasons (panel A in Figure; Supplementary Table 2). Statistically significant increases were also found among patients diagnosed with respiratory/cardiovascular diseases and for influenza/pneumonia (panels B and C in Figure; Supplementary Table 2).

A significant increase was also observed among infants and children <5 years and adults ≥65 years with all diagnoses (panel A in Figure; Supplementary Table 2). The increase in the monthly mean rate of hospitalization days was statistically significant for respiratory/cardiovascular diseases in most age groups, except the 35-64 age groups (panel B in Figure; Supplementary Table 2). A statistically significant increase in the monthly mean rate of hospitalization days for influenza/pneumonia was seen in all age groups except for the 15-24 age group (panel C in Figure; Supplementary Table 2).

Children <5 years of age showed the largest increases during the influenza season as compared with the summer, with an up to 155.9% increase in the mean monthly rate of hospitalization days due to influenza/pneumonia (panel C in Figure; Supplementary Table 2), and an up to 206.6% increase for respiratory/cardiovascular diseases in infants <1 year of age (panel B in Figure; Supplementary Table 2). In adults, the largest increases were observed among those

TABLE 2. Mean Monthly Length of Stay per Discharge During Influenza Season Compared With the Preceding Summer, 2005-2013 (contunued)

Age (Years)	Diagnoses (ICD9 code)	Summer Mean (SD)	Influenza Mean (SD)	Absolute Difference Between Influenza and Preceding Summer Season (Days)	Difference Between Influenza and Preceding Summer Season (%)	Wilcoxon *P* Value
35-44	All	3.13 (0.16)	3.20 (0.19)	0.07	2.2	.24
	Resp/Cardio (390-519)	3.67 (0.26)	3.66 (0.31)	–0.01	–0.2	.89
	Flu/Pneumo (480-487)	5.19 (0.78)	4.91 (0.60)	–0.28	–5.3	.34
45-54	All	3.42 (0.19)	3.50 (0.18)	0.08	2.3	.2
	Resp/Cardio (390-519)	3.78 (0.28)	3.82 (0.24)	0.05	1.3	.41
	Flu/Pneumo (480-487)	6.59 (0.95)	5.77 (0.93)	–0.82	–12.4	<.01
55-64	All	3.89 (0.24)	3.94 (0.28)	0.05	1.4	.57
	Resp/Cardio (390-519)	4.14 (0.33)	4.18 (0.31)	0.04	1.0	.5
	Flu/Pneumo (480-487)	7.28 (0.98)	6.22 (0.56)	–1.06	–14.6	<.001
65-74	All	4.42 (0.21)	4.54 (0.21)	0.12	2.6	.051
	Resp/Cardio (390-519)	4.63 (0.28)	4.74 (0.22)	0.11	2.3	.08
	Flu/Pneumo (480-487)	7.77 (0.89)	6.90 (0.54)	–0.87	–11.2	<.001
75-84	All	5.01 (0.23)	5.10 (0.29)	0.08	1.6	.3
	Resp/Cardio (390-519)	5.20 (0.29)	5.27 (0.31)	0.08	1.5	.3
	Flu/Pneumo (480-487)	8.03 (0.57)	7.65 (0.52)	–0.38	–4.7	.051
85+	All	5.31 (0.23)	5.40 (0.28)	0.08	1.5	.35
	Resp/Cardio (390-519)	5.56 (0.31)	5.62 (0.31)	0.05	1.0	.65
	Flu/Pneumo (480-487)	7.99 (0.88)	7.54 (0.64)	–0.45	–5.6	<.05

NOTE: Abbreviations: ICD9, International Classification of Diseases 9; SD, standard deviation.

≥75 years; the rates for influenza/pneumonia increased by about 40% (panel C in Figure; Supplementary Table 2), and the rates for respiratory/cardiovascular diseases increased by 14.8%-20.7% as compared with the summer months (panel B in Figure; Supplementary Table 2).

Statistically significant decreases in monthly mean rate of hospitalization days during influenza seasons were observed for all diagnoses in the 5-54 age groups (panel A in Figure; Supplementary Table 2). Decreases were not seen for the diagnoses of respiratory/cardiovascular diseases or influenza/pneumonia (panels B and C in Figure; Supplementary Table 2).

Hospital Length of Stay

The longest mean monthly LOS due to all diagnoses (for both influenza and summer seasons) was observed in adults ≥65 years of age (Table 2). The longest mean monthly LOS due to influenza/pneumonia (for both influenza and summer seasons) was observed in adults ≥55 years or older, and for the diagnosis of respiratory/cardiovascular diseases, infants <1 year and adults ≥55 years had the longest LOS.

The differences between influenza and summer seasons in mean monthly LOS were mostly small or not observed in any of the diagnostic categories examined. The mean monthly LOS due to a diagnosis of influenza/pneumonia was shorter during the influenza seasons than summer seasons in most age groups. These differences were statistically significant in children <5 years and adults ≥45 years (Table 2).

The mean LOS due to respiratory/cardiovascular diseases was significantly shorter during influenza seasons than summer seasons in children under 5.

Bed Occupancy

Mean bed occupancy was significantly higher during influenza seasons compared with the preceding summer seasons,

TABLE 3. Bed Occupancy Rates in Internal Medicine and Pediatric Departments During Influenza Season Compared With the Preceding Summer, by Year 2005-2013 (Percent)

	Internal Medicine Departments				Pediatric Departments			
Season	Summer	Influenza Season	Difference	*P* Value	Summer	Influenza Season	Difference	*P* Value
2005/6	101.2	107.8	6.6	<.001	82.9	92.1	9.2	<.001
2006/7	96.1	112.4	16.3	<.001	75.5	101.6	26.1	<.001
2007/8	94.9	105.6	10.7	<.001	79.7	95.7	16.0	<.001
2008/9	95.6	101.8	6.2	<.001	79.8	89.7	9.9	<.001
2010/11	99.2	102.2	3.0	<.001	80.9	96.3	15.4	<.001
2011/12	95.2	104.0	8.8	<.001	77.0	88.7	11.7	<.001
2012/13	96.9	103.8	6.9	<.001	73.5	91.7	18.2	<.001
Mean for the Period 2005-2013	96.9	104.7	7.8	<.001	78.7	93.2	14.5	<.001

both in internal medicine and pediatric departments (Table 3). The differences were higher in pediatric departments as compared with internal medicine departments for most years evaluated.

DISCUSSION

Our study demonstrates trends of excess hospitalizations during influenza as compared with summer seasons and identifies patient groups that contribute mostly to changes in hospital burden between these seasons.

Overall, the present study demonstrates differences between influenza and summer seasons for all measures tested: hospitalizations, hospitalization days, LOS, and bed occupancy. These differences were due primarily to excess number of hospitalizations and hospitalization days, rather than to longer LOS.

Our results concerning hospitalizations for all diagnoses are consistent with a United States report showing about 5% more hospitalizations following emergency department visits during winter compared with summer.[12]

The increase in hospitalizations and total hospitalization days in older age groups reflects the probability of severe diseases in a population with multiple comorbidities, and is consistent with a 90% influenza-related mortality due to respiratory and cardiovascular diseases reported in patients 65 and older.[13] The increase in hospitalization and total hospitalization days in the age groups <5 years during influenza seasons are consistent with studies showing that the risk of children to contract influenza is higher than that of adults surrounding them. In this regard, outbreak investigations during the 2009 influenza pandemic showed that influenza attack rates in children were higher than those of adults.[14]

Nationwide studies from Singapore and Taiwan also showed more hospitalizations related to influenza in young children and older adults.[15,16]

The increase in hospitalization days for all patients should be interpreted while taking into account the mean monthly LOS per patient (Table 2). In most age groups, a small decrease in the mean LOS for individual patients with the diagnosis of influenza/pneumonia was observed (Table 2). This decrease may suggest a need to shorten hospitalization slightly in order to accommodate new patients. Similarly, the decrease in hospitalization rates from all diagnoses during influenza seasons in the 5-54 years age groups (Figure) may stem, at least in part, from the shortage of available hospital beds due to patient overload. Additional study is required to further explore these decreases and their possible effects on morbidity and mortality.

Influenza vaccine guidelines in Israel following the 2009 influenza pandemic recommend influenza vaccination for all individuals age 6 months and older. However, influenza vaccination in Israel has remained low. Specifically, vaccination rates among children below the age of 5 years have been approximately 21%, as compared with 60%-65% in adults 65 years and over.[17] Given the low rate of vaccination in children, we believe that there would be minimal or no difference in hospitalization of children under the age of 5 years, between the pre- and postpandemic years. Israel has started a school-based influenza vaccination program for the 2016-2017 influenza season in an effort to increase childhood influenza vaccination. It would be important to see if the expansion and continuation of the program would have an effect on influenza season hospitalizations.

Our study has several advantages. To the best of our knowledge, it is the first study examining differences in hospital burden between influenza and summer seasons on a national level. As such, it constitutes one of the largest studies on the subject. In addition, our study relies on original data, rather than estimates. Analysis of specific months of each year in which influenza virus circulates provides a targeted analysis of influenza seasons, rather than the entire winter season. The comparison with summer months is of great importance for preparatory

plans by health systems, as it takes into account the degree of variation between the seasons. The analysis of 6 influenza seasons in our study intended to take into account season-to-season disease variability. Such variability among influenza seasons has been described previously due to changes in the virus itself, the population immune status, and the weather.[18]

We used several diagnosis categories to evaluate different aspects of hospital burden. Although the category of "all diagnoses" provided a broad assessment of hospital burden, influenza/pneumonia or pulmonary/cardiovascular disease constituted a more specific measure of influenza-associated burden.

Evaluating LOS added to the accuracy of hospital burden estimates, and our age-group analysis highlighted the specific age groups responsible for changes in hospital burden. Thus, the use of several measures to assess influenza season morbidity provides a comprehensive picture of the hospitalization dynamics between influenza and summer seasons. In this regard, the trends observed in our study for hospitalizations and total hospitalization days correspond to those observed in bed occupancy, especially for hospitalization rates due to all causes.

Our study has several limitations. We did not rely on laboratory diagnosis of influenza to determine burden. Because obtaining specimens for viral detection is usually based on individual clinical judgement, and patients hospitalized with influenza-related complications can often test negative for the virus due to time elapsed from disease onset, relying on a laboratory-based analysis may lead to underestimation of hospital burden. On the other hand, it is possible that patients with morbidity not specifically related to influenza were included in our analysis. Respiratory syncytial virus (RSV), for example, can also cause respiratory illness during the fall and winter.[19] However, in Israel, RSV epidemic usually occurs before the influenza epidemic.[17,20] Thus, it is expected that only a small percentage of hospital admissions due to RSV would occur during the influenza season. Another limitation of our study relates to the small number of months in the beginning and end of influenza seasons in which influenza activity was recorded only during part of the month. Thus, hospital burden may have been underestimated during these "incomplete" months. Future studies using time series analysis methods will contribute to a more accurate estimation of such differences, as well as account for variability in influenza activity.

Our results clearly highlight the issues that challenge hospitals in Israel, and possibly other countries, during influenza seasons, such as the most affected age groups and the shortening of hospital stay. Thus, our findings are most relevant for hospital preparedness towards influenza seasons, particularly in terms of the need for additional hospital beds and personnel.

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National Trends (2007-2013) of *Clostridium difficile* Infection in Patients with Septic Shock: Impact on Outcome

Kshitij Chatterjee, MD[1], Abhinav Goyal, MD[2], Aditya Chada, MD[3], Krishna Siva Sai Kakkera, MD[3], Howard L Corwin, MD[1,3]

[1]Department of Internal Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas; [2]Department of Internal Medicine, Einstein Medical Center, Philadelphia, Pennsylvania; [3]Division of Pulmonary and Critical Care Medicine, Department of Medicine, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

BACKGROUND: *Clostridium difficile* is the most common infectious cause of healthcare-associated diarrhea and is associated with worse outcomes and higher cost. Patients with septic shock (SS) are at increased risk of acquiring *C. difficile* infections (CDIs) during hospitalization, but little data are available on CDI complicating SS.

OBJECTIVE: Prevalence of CDI in SS between 2007-2013 and impact of CDI on outcomes in SS.

DESIGN: We used the National Inpatient Sample to identify hospitalizations (2007-2013) of adults with SS and CDI and the Nationwide Readmissions Database 2013 to calculate 30-day readmissions.

MAIN MEASUREMENTS: Outcomes were prevalence of CDI in SS, effect on mortality, length of stay (LOS), and 30-day readmission.

RESULTS: There were 2,031,739 hospitalizations with SS (2007-2013). CDI was present in 8.2% of SS. The in-hospital mortality of SS with and without CDI were comparable (37.1% vs 37.0%; $P = 0.48$). Median LOS was longer for SS with CDI (13 days vs 9 days; $P < 0.001$). LOS >75th percentile (>17 days) was 36.9% in SS with CDI vs 22.7% without CDI ($P < 0.001$). Similarly, LOS > 90th percentile (> 29 days) was 17.5% vs 9.1%, $P < 0.001$. Odds of LOS >75% and >90% in SS were greater with CDI (odds ratio [OR] 2.11; 95% confidence interval [CI], 2.06-2.15; $P < 0.001$ and OR 2.25; 95% CI, 2.22-2.28; $P < 0.001$, respectively). Hospital readmission of SS with CDI was increased, adjusted OR 1.26 (95% CI, 1.22-1.31; $P < 0.001$).

CONCLUSIONS: CDI complicating SS is common and is associated with increased hospital LOS and 30-day hospital readmission. This represents a population in which a focus on prevention and treatment may improve clinical outcomes. *Journal of Hospital Medicine* 2017;12:717-722. © 2017 Society of Hospital Medicine

Clostridium difficile infection (CDI) is the most common infectious cause of healthcare-associated diarrhea.[1] Development of a CDI during hospitalization is associated with increases in morbidity, mortality, length of stay (LOS), and cost.[2-5] The prevalence of CDI in hospitalized patients has increased dramatically from the mid-1990s to the mid-2000s to almost 9 cases per 1000 discharges; however, the CDI rate since 2007 appears to have plateaued.[6,7] Antibiotic use has historically been the most important risk factor for acquiring CDI; however, use of acid-suppressing agents, chemotherapy, chronic comorbidities, and healthcare exposure all also increase the risk of CDI.[7-10] The elderly (> 65 years of age) are particularly at risk for developing CDI and having worse clinical outcomes with CDI.[6,7]

Patients with septic shock (SS) often have multiple CDI risk factors (in particular, extensive antibiotic exposure) and thus, represent a population at a particularly high risk for acquiring a CDI during hospitalization. However, little data are available on the prevalence of CDI acquired in patients hospitalized with SS. We sought to determine the national-level temporal trends in the prevalence of CDI in patients with SS and the impact of CDI complicating SS on clinical outcomes between 2007 and 2013.

***Address for correspondence and reprint requests:** Kshitij Chatterjee, MD, 4301 W Markham Street, Little Rock, AR 72205; Telephone: 501-686-7000; Fax: 501-526-1774; E-mail: kchatterjee@uams.edu

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METHODS

Data Source

We used the National Inpatient Sample (NIS) and Nationwide Readmissions Database (NRD) for this study. The NIS is a database developed by the Agency of Healthcare Research and Quality for the Healthcare Cost and Utilization Project (HCUP).[11] It is the largest all-payer inpatient database in the United States and has been used by researchers and policy makers to analyze national trends in outcomes and healthcare utilization. The NIS database now approximates a 20% stratified sample of all discharges from all participating US hospitals. Sampling weights are provided by the manufacturer and can be used to produce national-level estimates. Following the redesign of the NIS in 2012, new sampling weights were provided for trend analysis for the years prior to 2012 to account for the new design. Every hospitalization is deidentified and converted into one unique entry that provides information on demographics, hospital characteristics, 1 primary and up to 24 secondary discharge diagnoses, comorbidities, LOS, in-hospital mortality, and procedures performed during stay. The discharge diagnoses are provided in the form of the *Inter-*

TABLE 1. Demographics, Hospital Characteristics, and Outcomes of Patients with SS with and without CDI

Demographics, Characteristics, and Outcomes	No CDI N = 1,865,307 (91.8%)	CDI N = 166,432 (8.2%)	*P* Value
Mean age, years (standard deviation)	66.8 (15.9)	69.8 (14.7)	<.001
Age categories, years			<.001
18 to 39	111,679 (6.0%)	6154 (3.7%)	
40 to 64	663,643 (35.6%)	48,413 (29.1%)	
65 to 79	627,430 (33.6%)	61,963 (37.2%)	
≥80	462,556 (24.8%)	49,903 (30.0%)	
Gender			<.001
Male	957,341 (51.3%)	81,004 (48.7%)	
Female	907,966 (48.7%)	85,429 (51.3%)	
Race			<.001
Caucasian	1273,312 (68.3%)	115,789 (69.6%)	
African-American	272,136 (14.6%)	24,531 (14.7%)	
Hispanic	188,940 (10.1%)	15,275 (9.2%)	
Other	130,918 (7.0%)	10,837 (6.5%)	
Teaching status	910,119 (48.8%)	75,675 (45.5%)	<.001
Non-teaching	942,111 (50.5%)	89,781 (53.9%)	
Teaching			
Hospital location			<.001
Rural	128,723 (6.9%)	7375 (4.4%)	
Urban	1723,506 (92.4%)	158,081 (95.0%)	
Hospital region			<.001
Northeast	398,917 (21.4%)	42,848 (25.7%)	
Midwest	297,510 (15.9%)	27,298 (16.4%)	
South	716,897 (38.4%)	55,962 (33.6%)	
West	451,983 (24.2%)	40,325 (24.2%)	
Hospital-bed size	177,541 (9.5%)	15,738 (9.5%)	.006
Small	469,389 (25.2%)	42,521 (25.5%)	
Medium	1,205,300 (64.6%)	107,198 (64.4%)	
Large			
Number of Charlson-Deyo comorbidities			<.001
0	329,805 (17.7%)	28,242 (17.0%)	
1	354,032 (19.0%)	31,031 (18.6%)	
2 or more	1,181,470 (63.3%)	107,160 (64.4%)	
In-hospital mortality	689,964 (37.0%)	61,708 (37.1%)	0.478
Median length of stay, days	9	13	<.001

NOTE: Abbreviations: CDI, *Clostridium difficile* infection; SS, septic shock.

national Classification of Diseases, 9th Revision-Clinical Modification (ICD-9-CM) codes.

The NRD is a database developed for HCUP that contains about 35 million discharges each year and supports readmission data analyses. In 2013, the NRD contained data from 21 geographically diverse states, accounting for 49.1% of all US hospitalizations. Diagnosis, comorbidities, and outcomes are presented in a similar manner to NIS.

Study Design

This was a retrospective cohort study. Data from the NIS between 2007 and 2013 were used for the analysis. Demographic data obtained included age, gender, race, Charlson-Deyo Comorbidity Index,[12] hospital characteristics (hospital region, hospital-bed size, urban versus rural location, and teaching status), calendar year, and use of mechanical ventilation. Cases with information missing on key demographic variables (age, gender, and race) were excluded. Only adults (>18 years of age) were included for the analysis.

SS was identified by either (1) ICD-9-CM diagnosis code for SS (785.52) or (2) presence of vasopressor use (00.17) along with ICD-9-CM codes of sepsis, severe sepsis, septicemia, bacteremia, or fungemia. This approach is consistent with what has been utilized in other studies to identify cases

TABLE 2. Temporal Trends of Prevalence of CDI Among Hospitalizations with SS

Year	Number of SS Observations	Number of CDI Observations Among SS	Prevalence of CDI
2007	179,284	14,912	8.3
2008	222,943	18,133	8.1
2009	259,258	21,922	8.5
2010	298,017	23,267	7.8
2011	331,663	28,488	8.6
2012	354,550	28,950	8.2
2013	386,025	30,760	8.0
All years	2,031,739	166,432	8.2

NOTE: All frequencies are weighted and represent national estimates. Abbreviations: CDI, *Clostridium difficile* infection; SS, septic shock.

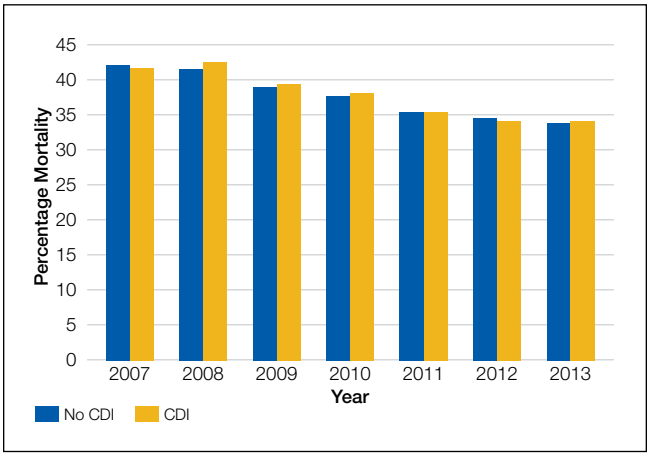

FIG 1. Temporal trends of mortality among patients with SS with and without associated CDI. NOTE: Abbreviations: CDI, *Clostridium difficile* infection; SS, septic shock.

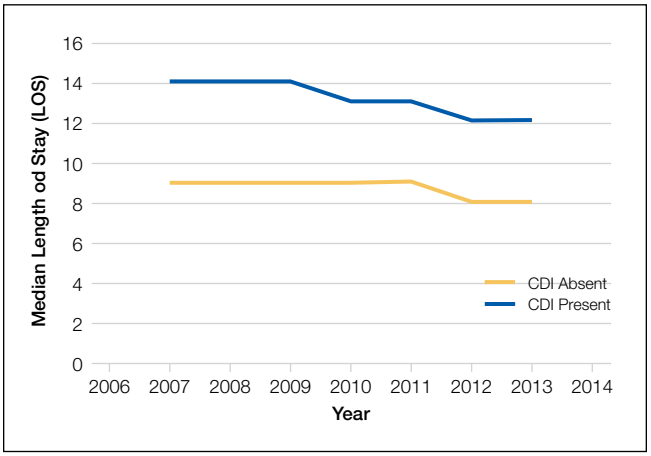

FIG 2. Temporal trends of LOS among hospitalizations with SS with and without CDI. Median LOS is represented in days. NOTE: Abbreviations: CDI, *Clostridium difficile* infection; LOS, length of stay; SS, septic shock.

of sepsis or SS from administrative databases.[13-15] The appendix provides a complete list of ICD-9-CM codes used in the study. CDI was identified by ICD-9-CM code 008.45 among the secondary diagnosis. This code has been shown to have good accuracy for identifying CDI using administrative data.[16] To minimize the inclusion of cases in which a CDI was present at admission, hospitalizations with a primary diagnosis of CDI were not included as cases of CDI complicating SS.

We used NRD 2013 for estimating the effect of CDI on 30-day readmission after initial hospitalizations with SS. We used the criteria for index admissions and 30-day readmissions as defined by the Centers for Medicare and Medicaid Services. We excluded patients who died during their index admission, patients with index discharges in December due to a lack of sufficient time to capture 30-day readmissions, and patients with missing information on key variables. We also excluded patients who were not a resident of the state of index hospitalization since readmission across state boundaries could not be identified in NRD. Manufacturer provided sampling weights were used to produce national level estimates. The cases of SS and CDI were identified by ICD-9-CM codes using the methodology described above.

Outcomes

Our primary outcome of interest was the total and yearly prevalence of CDI in patients with SS from 2007 to 2013. The secondary outcomes were mortality, LOS, and 30-day readmissions in patients with SS with and without CDI.

Statistical Analysis

Weighted data from NIS were used for all analyses. Demographics, hospital characteristics, and outcomes of all patients with SS were obtained. The prevalence of CDI was calculated for each calendar year. The temporal trends of outcomes (LOS and in-hospital mortality) of patients were

plotted for patients with SS with and without CDI. A χ^2 test of trend for proportions was used with the Cochran-Armitage test to calculate statistical significance of changes in prevalence. To test for statistical significance of the temporal trends of LOS, a univariate linear regression was used, with calendar year as a covariate. Independent samples t test, a Mann-Whitney *U* test, and a χ^2 test were used to determine statistical significance of parameters between the group with CDI and the group without CDI.

Prolonged LOS was defined either as a LOS > 75th or > 90th percentile of LOS among all patients with SS. To identify if CDI was associated with a prolonged LOS after adjusting for patient and hospital characteristics, a multivariate logistic regression analysis was used. Variables included in the regression model were age, gender, race, Charlson-Deyo Comorbidity Index, hospital characteristics (hospital region, hospital-bed size, urban versus rural location, and teaching status), calendar year, and use of mechanical ventilation. Data on cases were available for all the above covariates except hospital characteristics, such as teaching status, location, and bed size (these were missing for 0.7% of hospitals).

Stata 13.1.0 (Stata Corp, College Station, TX) and SPSS 23.0 (SPSS Inc., Chicago, IL) were used to perform statistical analyses. A *P* value of <0.05 was considered statistically significant.

RESULTS

Demographics

A total of 2,031,739 hospitalizations of adults with SS were identified between 2007 and 2013. CDI was present in 166,432 (8.2%) of these patients. Demographic data are displayed in Table 1. CDI was more commonly observed in elderly patients (> 65 years) with SS; 9.3% among the elderly versus 6.6% among individuals < 65 years; $P < 0.001$. The prevalence of CDI was greater in urban than in rural hospitals (8.4% vs 5.4%; $P < 0.001$) and greater in teaching than in nonteaching hospitals (8.7% vs 7.7%; $P < 0.001$). The prevalence of CDI in SS remained stable between 2007 and 2013 (Table 2).

Mortality

In the overall study cohort, the in-hospital mortality for SS was 37%. The in-hospital mortality rate of patients with SS complicated by a CDI was comparable to the mortality rate of patients without a CDI (37.1% vs 37.0%; $P = 0.48$). The mortality of patients with SS, with or without CDI, progressively decreased from 2007 to 2013 (*P* value for trend < 0.001 for each group; Figure 1).

Length of Stay

The median LOS for all patients with SS was 9 days. Patients with CDI had a longer median LOS than did those without CDI (13 vs 9 days; $P < 0.001$). Between 2007 and 2013, the median LOS of CDI group decreased from 14 to 12 days ($P < 0.001$) while that of non-CDI group decreased from 9 to 8 days ($P < 0.001$; Figure 2). We also examined LOS among subgroups who were discharged alive and those who died during hospitalization. For patients who were discharged alive, the LOS with and without CDI was 15 days versus 10 days, respectively ($P < 0.001$). For patients who died during hospitalization, LOS with and without CDI was 10 days versus 6 days, respectively ($P < 0.001$).

The 75th percentile of LOS of the total SS cohort was 17 days. An LOS > 17 days was observed in 36.9% of SS patients with CDI versus 22.7% without CDI (P < 0.001). After adjusting for patient and provider level variables, the odds of a LOS > 17 days were significantly greater for SS patients with CDI (odds ratio [OR] 2.11; 95% confidence interval [CI], 2.06-2.15; $P < 0.001$).

The 90th percentile of LOS of the total SS cohort was 29 days. An LOS > 29 days was observed in 17.5% of SS patients with a CDI versus 9.1% without a CDI ($P < 0.001$). After adjustment for patient and provider level variables, the odds of a LOS > 29 days were significantly greater for SS patients with a CDI (OR 2.25; 95% CI, 2.22-2.28; $P < 0.001$).

Hospital Readmission

In 2013, patients with SS and CDI had a higher rate of 30-day readmission as compared to patients with SS without CDI (9.8% vs 7.4% respectively; $P < 0.001$). The multivariate adjusted OR for 30-day readmission for patients with SS and a CDI was 1.26 (95% CI, 1.22-1.31; $P < 0.001$).

Additional Analyses

Lastly, we performed an additional analysis to confirm our hypothesis that a CDI by itself is rarely a cause of SS, and that CDI as the principal diagnosis would constitute an extremely low number of patients with SS in an administrative dataset. In NIS 2013, there were 105,750 cases with CDI as the primary diagnosis. A total of 4470 (4.2%) had a secondary diagnosis of sepsis and only 930 (0.9%) cases had a secondary diagnosis of SS.

DISCUSSION

This is the first study to report on the prevalence and outcome of CDI complicating SS. By using a large nationally representative sample, we found CDI was very prevalent among individuals hospitalized with SS and, at a level in excess of that seen in other populations. Of interest, we did not observe an increase in mortality of SS when complicated by CDI. On the other hand, patients with SS complicated by CDI were more much likely to have a prolonged hospital LOS and a higher risk of 30-day hospital readmission.

The prevalence of CDI exploded between the mid-1990s and mid-2000s, including community, hospital, and intensive care unit (ICU)–related disease.[6,7,17-20] Patients with SS often have multiple risk factors associated with CDI and thus represent a high-risk population for developing CDI.[7] Our findings are consistent with the suggestion that individuals with SS are at a higher risk of developing CDI. Compared to the rate of CDI in all hospitalized patients, our data sug-

gest an almost 10-fold increase in CDI rate for patients with SS.[6] Patients with SS and CDI may account for as much as 10% of total CDIs.[6,7] As has been reported for CDI in general, we observed that CDI complicating SS was more common in those > 65 years of age.[4,21] The prevalence of CDI we observed in patients with SS was also higher than has been reported in ICU patients in general (1%), and higher than reported for patients requiring mechanical ventilation (6.6%), including prolonged mechanical ventilation (5.3%); further supporting the conclusion that patients with SS are a particularly high-risk group for acquiring CDI, even compared with other ICU patients.[20,22,23] Similarly, the rate of CDI among SS was 8 times higher than that of recently reported hospital-onset CDI among patients with sepsis in general (incidence 1.08%).[24] We have no data regarding why patients with SS have a higher rate of CDI; however, the intensity and duration of antibiotic treatment of these patients may certainly play a role.[25] It has recently been reported that CDI in itself can be a precursor leading to intestinal dysbiosis that can increase the risk of subsequent sepsis. Similarly, patients with SS may have higher prevalence of dysbiosis that, in turn, might predispose them to CDI at a higher rate than other individuals.

Following the increase in CDIs in the mid-1990s and the mid-2000s, since 2007 the overall prevalence of CDIs has been stable, albeit at the higher rate. More recently, the Centers for Disease Control and Prevention (CDC) has reported a decrease in hospital onset CDI after 2011.[26]

The finding that CDI in SS patients was not associated with an increase in mortality is consistent with other reports of CDI in ICU patients in general as well as higher-risk ICU populations such as patients requiring mechanical ventilation, including those on long-term mechanical ventilator support.[17,18,20,22,23] Why the mortality of ICU patients with CDI is not increased is not completely clear. It has been suggested that this may be related to early recognition and treatment of CDI developing in the ICU.[22] Along these lines, it has been previously observed that for patients with CDI on mechanical ventilation, patients who were transferred to the ICU from the ward had worse clinical outcomes compared to patients directly admitted to the ICU, likely due to delayed recognition and treatment in the former.[22] Similarly, ICU patients in whom CDI was identified prior to ICU admission had more severe CDI, and mortality that was directly related to CDI was only observed in patients who had CDI identified pre-ICU transfer.[18] The increase in mortality observed in patients with sepsis in general with CDI may reflect similar factors.[24] We observed a trend of decreasing mortality in SS patients with or without CDI during 2007 to 2013 consistent to what has been generally reported in SS.[13,14]

The increase in LOS observed in SS patients with CDI is also consistent with what has been observed in other ICU populations, as well as in patients with sepsis in general.[17,22-24] Of note, in addition to the increase in median LOS, we found a significant increase in the number of patients with a prolonged LOS associated with having SS with CDI. It is important to note that development of CDI during hospitalization is affected by pre-CDI hospital LOS, so prolonged LOS may not be solely attributable to CDI. The interaction between LOS and CDI remains complex in which higher LOS might be associated with higher incidence of CDI occurrence, and once established, CDI might be associated with changes in LOS for the remaining hospitalization.

Hospitalized patients with CDI have an overall higher resource utilization than those without CDI.[27] A recent review has estimated the overall attributable cost of CDI to be $6.3 billion; the attributable cost per case of hospital acquired CDI being 1.5 times the cost of community-acquired CDI.[5] We did not look at cost directly. However, in the high-CDI risk ICU population requiring prolonged mechanical ventilation, those with CDI had a substantial increase in total costs.[23] Given the substantial increase in LOS associated with CDI complicating SS, there would likely be a significant increase in hospital costs related to providing care for these patients. Further adding to the potential burden of CDI is our finding that CDI and SS was associated with an increase in 30-day hospital readmission rate. This is consistent with a recent report that ICU patients with CDI who are discharged from the hospital have a 25% 30-day hospital readmission rate.[28] However, we do not have data either as to the reason for hospital readmission or whether the initial CDI or CDI recurrence played a role. This suggests that, in addition to intervention directed toward preventing CDI, efforts should be directed towards identifying factors that can be modified in CDI patients prior to or after hospital discharge.

This study has several limitations. Using an administrative database (such as NIS) has an inherent limitation of coding errors and reporting bias can lead to misclassification of cohort definition (SS) and outcome (CDI). To minimize bias due to coding errors, we used previously validated ICD-9-CM codes and approach to identify individuals with SS and CDI.[13-15] Although the SS population was identified with ICD-9-CM codes using an administrative database, the in-hospital mortality for our septic population was similar to previously reported mortality of SS, suggesting the population selected was appropriate.[13] SS due to CDI could not be identified; however, CDI by itself causing SS is rare, as described in recent literature.[29,30] An important potential bias that needs to be acknowledged is the immortal time bias. The occurrence of CDI in itself can be influenced by pre-CDI hospital LOS. Patients who were extremely sick could have died early in their hospital course before they could acquire CDI, which would influence the mortality difference between the group with CDI and group without CDI. Furthermore, we did not have information on either the treatment of CDI or SS or any measures of severity of illness, which could lead to residual confounding despite adjusting for multiple variables. In terms of readmission data, it was necessary to exclude nonresidents of a state for the 30-day readmission analysis, as readmissions could not be tracked across state boundaries by using the NRD. This might have resulted in an underrepresentation of the readmission burden.

Lastly, it was not possible to identify mortality after hospital discharge as the NIS provides only in-hospital mortality.

In conclusion, CDI is more prevalent in SS than are other ICU populations or the hospital population in general, and CDI complicating SS is associated with significant increase in LOS and risk of 30-day hospital readmission. How much of the increase in resource utilization and cost are in fact attributable to CDI in this population remains to be studied. Our finding of high prevalence of CDI in the SS population further emphasizes the importance of maintaining and furthering approaches to reduce incidence of hospital acquired CDI. While reducing unnecessary antibiotics is important, a multipronged approach that includes education and infection control interventions has also been shown to reduce the incidence of CDI in the ICU.[31] Given the economic burden of CDI, implementing these strategies to reduce CDI is warranted. Similarly, the risk of 30-day hospital readmission with CDI highlights the importance of identifying the factors that contribute to hospital readmission prior to initial hospital discharge. Programs to reduce CDI will not only improve outcomes directly attributable to CDI but also decrease the reservoir of CDI. Finally, to the extent that CDI can be reduced in the ICU, the utilization of ICU resources will be more effective.

Disclosure: No conflicts of interest or financial disclosures to report. Author Contributions: KC had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. KC, AG, AC, KK, and HC contributed to study design, data analysis, interpretation, and the writing of the manuscript. Guarantor statement: Kshitij Chatterjee takes responsibility for (is the guarantor of) the content of the manuscript, including the data and analysis.

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Appropriate Reconciliation of Cardiovascular Medications After Elective Surgery and Postdischarge Acute Hospital and Ambulatory Visits

Jonathan S. Lee, MD, MAS[1]*, Ralph Gonzales, MD, MSPH[1], Eric Vittinghoff, PhD[2], Kitty K. Corbett, PhD, MPH[3], Kirsten E. Fleischmann, MD[4], Neil Sehgal, PhD, MPH[5], Andrew D. Auerbach, MD, MPH[5]

[1]Division of General Internal Medicine, University of California San Francisco, San Francisco, California; [2]Department of Epidemiology and Biostatistics, University of California San Francisco, San Francisco, California; [3]School of Public Health and Health Systems, University of Waterloo, Waterloo, Ontario, Canada; [4]Division of Cardiology, University of California San Francisco, San Francisco, California; [5]Division of Hospital Medicine, University of California San Francisco, San Francisco, California.

BACKGROUND: Few studies have assessed the quality and impact of postoperative cardiovascular medication reconciliation.

OBJECTIVE: To describe appropriate discharge reconciliation of cardiovascular medications and assess associations with postdischarge healthcare utilization in surgical patients.

DESIGN: Retrospective cohort study from January 2007 to December 2011.

SETTING: An academic medical center.

PATIENTS: Seven hundred and fifty-two adults undergoing elective noncardiac surgery and taking antiplatelet agents, beta-blockers, renin-angiotensin system inhibitors, or statin lipid-lowering agents before surgery.

MEASUREMENTS: Primary predictor: appropriate discharge reconciliation of preoperative cardiovascular medications (continuation without documented contraindications). Primary outcomes: acute hospital visits (emergency department visits or hospitalizations) and unplanned ambulatory visits (primary care or surgical) at 30 days after surgery.

RESULTS: Preoperative medications were appropriately reconciled in 436 (58.0%) patients. For individual medications, appropriate discharge reconciliation occurred for 156 of the 327 patients on antiplatelet agents (47.7%), 507 of the 624 patients on beta-blockers (81.3%), 259 of the 361 patients on renin-angiotensin system inhibitors (71.8%), and 302 of the 406 patients on statins (74.4%). In multivariable analyses, appropriate reconciliation of all preoperative medications was not associated with acute hospital (adjusted odds ratio [AOR], 0.94; 95% confidence interval [CI], 0.63-1.41) or unplanned ambulatory visits (AOR, 1.48; 95% CI, 0.94-2.35). Appropriate reconciliation of statin therapy was associated with lower odds of acute hospital visits (AOR, 0.47; 95% CI, 0.26-0.85). There were no other statistically significant associations between appropriate reconciliation of individual medications and either outcome.

CONCLUSIONS: Although large gaps in appropriate discharge reconciliation of chronic cardiovascular medications were common in patients undergoing elective surgery, these gaps were not consistently associated with postdischarge acute hospital or ambulatory visits. *Journal of Hospital Medicine* 2017;12:723-730. © 2017 Society of Hospital Medicine

Medication reconciliation at hospital discharge is a critical component of the posthospital transition of care.[1] Effective reconciliation involves a clear process for documenting a current medication list, identifying and resolving discrepancies, and then documenting decisions and instructions around which medications should be continued, modified, or stopped.[2] Existing studies[3-5] suggest that medication discrepancies are common during hospital discharge transitions of care and lead to preventable adverse drug events, patient disability, and increased healthcare utilization following hospital discharge, including physician office visits, emergency department (ED) visits, and hospitalizations.[6-8]

While the majority of studies of medication discrepancies have been conducted in general medical patients, few have examined how gaps in discharge medication reconciliation might affect surgical patients.[9,10] Two prior studies[9,10] suggest that medication discrepancies may occur more frequently for surgical patients, compared with medical patients, particularly discrepancies in reordering home medications postoperatively, raising patient safety concerns for more than 50 million patients hospitalized for surgery each year.[11] In particular, little is known about the appropriate discharge reconciliation of chronic cardiovascular medications, such as beta-blockers, renin-angiotensin system inhibitors, and statins in surgical patients, despite perioperative practice guidelines recommending continuation or rapid reinitiation of these medications after noncardiac surgery.[12] Problems with chronic cardiovascular medications have been implicated as major contributors to ED visits and hospitalizations for adverse drug events,[13,14] further highlighting the importance of safe and appropriate management of these medications.

To better understand the current state and impact of post-

***Address for correspondence and reprint requests:** Jonathan S. Lee, MD, University of California, San Francisco, 1545 Divisadero Street, 2nd Floor, San Francisco, CA 94143-0320; Telephone: 415-353-7900; Fax: 415-353-2640; E-mail: jonathan.lee2@ucsf.edu.

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TABLE 1. Characteristics of Patients Hospitalized for Elective Noncardiac Surgery by Appropriate Cardiovascular Medication Reconciliation at Discharge[a]

	Discharge Medication Reconciliation		
Patient Characteristics	Appropriate N=436	Inappropriate N=316	*P* Values
Demographics			
Age (y), mean (SD)	61.6 (11.8)	61.4 (12.0)	.76
Male, n (%)	211 (48.4)	172 (54.4)	.10
Race and ethnicity, n (%)			.89
White, non-Hispanic	315 (72.3)	231 (73.1)	
Black, non-Hispanic	28 (6.4)	23 (7.3)	
Hispanic	36 (8.3)	22 (7.0)	
Other[b]	57 (13.1)	40 (12.7)	
Surgical service, n (%)	110 (25.2)	63 (19.9)	<.001
General surgery	106 (24.3)	52 (16.5)	
Orthopedic surgery	91 (20.9)	58 (18.4)	
Neurosurgery	34 (7.8)	60 (19.0)	
Urological surgery	23 (5.3)	8 (2.5)	
Vascular surgery	22 (5.1)	17 (5.4)	
Gynecology/oncology	21 (4.8)	40 (12.7)	
Renal/liver transplant surgery	14 (3.2)	8 (2.5)	
Cardiothoracic surgery	9 (2.1)	2 (0.6)	
Plastic surgery	6 (1.4)	8 (2.5)	
Otolaryngology			
Surgical cardiovascular risk			
Revised cardiac risk index score, n (%)			.02
0	282 (64.7)	167 (52.9)	
1	110 (25.2)	113 (35.8)	
2	34 (7.8)	27 (8.5)	
3	8 (1.8)	8 (2.5)	
4	2 (0.5)	1 (0.3)	
Individual risk index criteria, n (%)			
High-risk surgery	5 (1.2)	1 (0.3)	.21
History of insulin-dependent diabetes	33 (7.6)	33 (10.4)	.17
Baseline creatinine > 2 mg/dL	53 (12.2)	66 (20.9)	.001
History of myocardial infarction	51 (11.7)	47 (14.9)	.20
History of stroke	36 (8.3)	33 (10.4)	.31
History of heart failure	32 (7.3)	15 (4.8)	.15
Preoperative medication use, n (%)[c]			
Antiplatelet agent	122 (28.0)	205 (64.9)	<.001
Beta-blocker	371 (85.1)	253 (80.1)	.07
Renin-angiotensin inhibitor	184 (42.2)	177 (56.0)	<.001
Statin	211 (48.4)	195 (61.7)	<.001
Number of cardiovascular medications			<.001
1	154 (35.3)	47 (14.9)	
2	151 (34.6)	89 (28.2)	
3	92 (21.1)	115 (36.4)	
4	39 (8.9)	65 (20.6)	

[a]Appropriate medication reconciliation at discharge for cardiovascular medications being taken in the preoperative period was defined as medical record documentation that the medication was being prescribed at discharge, or documentation of a new contraindication to the medication during hospitalization if it was not prescribed.

[b]Other race and ethnicity consisted of patients whose race was reported as Asian, Pacific Islander, Native American, or Alaskan Native, and patients with unreported race or ethnicity.

[c]Antiplatelet agents include aspirin, aspirin-dipyridamole, and clopidogrel, and renin-angiotensin system inhibitors include angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers.

operative discharge medication reconciliation of chronic cardiovascular medications in surgical patients, we examined (1) the appropriate discharge reconciliation of 4 cardiovascular medication classes, and (2) the associations between the appropriate discharge reconciliation of these medication classes and postdischarge acute hospital and ambulatory vis-

TABLE 2. Frequency of Preoperative Cardiovascular Medication Use and Appropriate Medication Reconciliation at Discharge in Patients Hospitalized for Elective Noncardiac Surgery

Cardiovascular Medication[a]	Preoperative Frequency (N = 752) n (%)	Appropriate Reconciliation[b] n/N (%)
Antiplatelet agent	327 (43.5)	156/327 (47.7)
Beta-blocker	624 (83.0)	507/624 (81.3)
Renin-angiotensin system inhibitor	361 (48.0)	259/361 (71.8)
Statin	406 (54.0)	302/406 (74.4)
Number of cardiovascular medications		
1	201 (26.7)	154/201 (76.6)
2	240 (31.9)	151/240 (62.9)
3	207 (27.5)	92/207 (44.4)
4	104 (13.8)	39/104 (37.5)

[a]Antiplatelet agents include aspirin, aspirin-dipyridamole, and clopidogrel, and renin-angiotensin inhibitors include angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers.

[b]Appropriate medication reconciliation at discharge for cardiovascular medications being taken in the preoperative period was defined as medical record documentation that the medication was being prescribed at discharge, or documentation of a new contraindication to the medication during hospitalization if it was not prescribed.

TABLE 3. Associations Between Appropriate Cardiovascular Medication Reconciliation at Discharge and ED Visits or Hospitalizations 30 Days After Surgery

	ED Visits or Hospitalizations 30 Days After Surgery (N = 679)		
Medication Reconciliation	n/N (%)	*P* Values	AOR (95% CI)[a]
Complete vs incomplete			
Inappropriate	66/295 (22.4)	.63	Reference
Appropriate	80/384 (20.8)		0.94 (0.63-1.41)
By medication			
Antiplatelet agent			
Inappropriate	32/161 (19.9)	.40	Reference
Appropriate	33/138 (23.9)		1.11 (0.61-2.03)
Beta-blocker			
Inappropriate	25/106 (23.6)	.71	Reference
Appropriate	100/456 (21.9)		0.95 (0.57-1.60)
Renin-angiotensin system inhibitor			
Inappropriate	19/95 (20.0)	.93	Reference
Appropriate	44/225 (19.6)		1.06 (0.55-2.03)
Statin			
Inappropriate	30/94 (31.9)	.004	Reference
Appropriate	50/279 (17.9)		0.47 (0.26-0.85)

[a]Odds ratios represent the odds of ED visits or hospitalizations within 30 days of surgery for appropriate (vs inappropriate) reconciliation of cardiovascular medications at discharge, adjusted for age, sex, race/ethnicity, revised cardiac risk index risk factors, the number of preoperative cardiovascular medication classes, surgical service, and clustering by attending physician.

NOTE: Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; ED, emergency department.

its in patients hospitalized for elective noncardiac surgery at an academic medical center.

METHODS

Study Design and Patient Selection

We performed a retrospective analysis of data collected as part of a cohort study of hospitalized surgical patients admitted between January 2007 and December 2011. The original study was designed to assess the impact of a social marketing intervention on guideline-appropriate perioperative beta-blocker use in surgical patients. The study was conducted at 1 academic medical center that had 2 campuses with full noncardiac operative facilities and a 600-bed total capacity. Both sites had preoperative clinics, and patients were recruited by review of preoperative clinic records. Institutional review boards responsible for all sites approved the study.

For this analysis, we included adults (age >18 years) undergoing elective noncardiac surgery, who were expected

TABLE 4. Associations Between Appropriate Cardiovascular Medication Reconciliation at Discharge and Unplanned Ambulatory Visits 30 Days After Surgery

	Unplanned Ambulatory Visits 30 Days After Surgery (N = 679)		
Medication Reconciliation	n/N (%)	*P* Values	AOR (95% CI)[a]
Complete vs incomplete			
Inappropriate	41/295 (13.9)	.13	Reference
Appropriate	70/384 (18.2)		1.48 (0.94-2.35)
By Medication			
Antiplatelet agent			
Inappropriate	22/161 (13.7)	.37	Reference
Appropriate	24/138 (17.4)		1.25 (0.58-2.68)
Beta-blocker			
Inappropriate	17/106 (16.0)	.47	Reference
Appropriate	87/456 (19.1)		1.18 (0.65-2.15)
Renin-angiotensin system inhibitor			
Inappropriate	13/95 (13.7)	.37	Reference
Appropriate	40/225 (17.8)		1.32 (0.65-2.68)
Statin			
Inappropriate	14/94 (14.9)	.83	Reference
Appropriate	39/279 (14.0)		1.06 (0.48-2.32)

[a]Odds ratios represent the odds of unplanned primary care or surgical ambulatory visits within 30 days of surgery for appropriate (vs inappropriate) reconciliation of cardiovascular medications at discharge, adjusted for age, sex, race/ethnicity, revised cardiac risk index risk factors, the number of preoperative cardiovascular medication classes, surgical service, and clustering by attending physician.

NOTE: Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

to remain hospitalized for at least 1 day and were taking antiplatelet agents (aspirin, aspirin-dipyridamole, or clopidogrel), beta-blockers, renin-angiotensin system inhibitors (angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers), or statin lipid-lowering agents.

Data Collection

Data Sources. We collected data from a structured review of medical records as well as from discharge abstract information obtained from administrative data systems. Data regarding patient demographics (age, sex, and race/ethnicity), medical history, preoperative cardiovascular medications, surgical procedure and service, and attending surgeon were obtained from a medical record review of comprehensive preoperative clinic evaluations. Data regarding complications during hospitalization were obtained from medical record review and administrative data (Supplement for *International Classification of Diseases, Ninth Revision* codes).[15] Research assistants abstracting data were trained by using a comprehensive reference manual providing specific criteria for classifying chart abstraction data. Research assistants also were directly observed during initial chart abstractions and underwent random chart validation audits by a senior investigator to ensure consistency. Any discrepancies in coding were resolved by consensus among senior investigators.

Definition of Key Predictor: Appropriate Reconciliation. We abstracted discharge medication lists from the electronic medical record. We defined the appropriate reconciliation of cardiovascular medications at discharge as documentation in discharge instructions, medication reconciliation tools, or discharge summaries that a preadmission cardiovascular medication was being continued at discharge, or, if the medication was not continued, documentation of a new contraindication to the medication or complication precluding its use during hospitalization. Medication continuity was considered appropriate if it was continued at discharge irrespective of changes in dosage. By using this measure for individual medications, we also assessed appropriate reconciliation as an "all-or-none" complete versus incomplete measure (appropriate reconciliation of all preoperative cardiovascular medication classes the patient was taking).[16]

Definition of Outcomes. Our coprimary outcomes were acute hospital visits (ED visits or hospitalizations) and unplanned ambulatory visits (primary care or surgical) at 30 days after surgery. Postoperative ambulatory visits that were not planned prior to surgery were defined as unplanned. Outcomes were ascertained by patient reports during follow-up telephone questionnaires administered by trained research staff and verified by medical record review.

Definition of Covariates. Using these data, we calculated a Revised Cardiac Risk Index (RCRI) score,[17] which estimates the risk of perioperative cardiac complications in patients undergoing surgery. Through chart abstraction data supplemented by diagnosis codes from administrative data, we also constructed variables indicating occurrences of postoperative complications anytime during hospitalization that might pose contraindications to continuation of the 4 cardiovascular medication classes studied. For example, if a

chart indicated that the patient had an acute rise in creatinine (elevation of baseline creatinine by 50% or absolute rise of 1 mg/dL in patients with baseline creatinine greater than 3 mg/dL) during hospitalization and a preoperative renin-angiotensin system inhibitor was not prescribed at discharge, we would have considered discontinuation appropriate. Other complications we abstracted were hypotension (systolic blood pressure less than 90 mmHg) for beta-blockers and renin-angiotensin system inhibitors, bradycardia (heart rate less than 50 bpm) for beta-blockers, acute kidney injury (defined above) and hyperkalemia for renin-angiotensin system inhibitors, and bleeding (any site) for antiplatelet agents.

Statistical Analysis

We used χ^2 and Kruskal-Wallis tests to compare baseline patient characteristics. To assess associations between appropriate medication reconciliation and patient outcomes, we used multilevel mixed-effects logistic regression to account for the clustering of patients by the attending surgeon. We adjusted for baseline patient demographics, surgical service, the number of baseline cardiovascular medications, and individual RCRI criteria. We constructed separate models for all-or-none appropriate reconciliation and for each individual medication class.

As a sensitivity analysis, we constructed similar models by using a simplified definition of appropriate reconciliation based entirely on medication continuity (continued or not continued at discharge) without taking potential contraindications during hospitalization into account. For complete versus incomplete reconciliation, we also constructed models with an interaction term between the number of baseline cardiovascular medications and appropriate medication reconciliation to test the hypothesis that inappropriate reconciliation would be more likely with an increasing number of preoperative cardiovascular medications. Because this interaction term was not statistically significant, we did not include it in the final models for ease of reporting and interpretability. We performed all statistical analyses using Stata 14 (StataCorp, LLC, College Station, Texas), and used 2-sided statistical tests and a *P* value of less than .05 to define statistical significance.

RESULTS

Patient Characteristics

A total of 849 patients were enrolled, of which 752 (88.6%) were taking at least 1 of the specified cardiovascular medications in the preoperative period. Their mean age was 61.5; 50.9% were male, 72.6% were non-Hispanic white, and 89.4% had RCRI scores of 0 or 1 (Table 1). The majority (63.8%) were undergoing general surgery, orthopedic surgery, or neurosurgery procedures. In the preoperative period, 327 (43.5%) patients were taking antiplatelet agents, 624 (83.0%) were taking beta-blockers, 361 (48.0%) were taking renin-angiotensin system inhibitors, and 406 (54.0%) were taking statins (Table 2). Among patients taking antiplatelet agents, 271 (82.9%) were taking aspirin alone, 21 (6.4%) were taking clopidogrel alone, and 35 (10.7%) were taking dual antiplatelet therapy with aspirin and clopidogrel. Nearly three-quarters of the patients (551, 73.3%) were taking medications from 2 or more classes, and the proportion of patients with inappropriate reconciliation increased with the number of preoperative cardiovascular medications.

Patients with and without appropriate reconciliation of all preoperative cardiovascular medications were similar in age, sex, and race/ethnicity (Table 1). Patients with inappropriate reconciliation of at least 1 medication were more likely to be on the urology and renal/liver transplant surgical services, have higher RCRI scores, and be taking antiplatelet agents, statins, renin-angiotensin system inhibitors, and 3 or more cardiovascular medications in the preoperative period.

Appropriate Medication Reconciliation

Four hundred thirty-six patients (58.0%) had their baseline cardiovascular medications appropriately reconciled. Among all patients with appropriately reconciled medications, 1 (0.2%) had beta-blockers discontinued due to a documented episode of hypotension; 17 (3.9%) had renin-angiotensin system inhibitors discontinued due to episodes of acute kidney injury, hypotension, or hyperkalemia; and 1 (0.2%) had antiplatelet agents discontinued due to bleeding. For individual medications, appropriate reconciliation between the preoperative and discharge periods occurred for 156 of the 327 patients on antiplatelet agents (47.7%), 507 of the 624 patients on beta-blockers (81.3%), 259 of the 361 patients on renin-angiotensin system inhibitors (71.8%), and 302 of the 406 patients on statins (74.4%; Table 2).

Associations Between Medication Reconciliation and Outcomes

Thirty-day outcome data on acute hospital visits were available for 679 (90.3%) patients. Of these, 146 (21.5%) were seen in the ED or were hospitalized, and 111 (16.3%) were seen for an unplanned primary care or surgical outpatient visit at 30 days after surgery. Patients with incomplete outcome data were more likely to have complete medication reconciliation compared with those with complete outcome data (71.2% vs 56.6%, $P = 0.02$). As shown in Table 3, the proportion of patients with 30-day acute hospital visits was nonstatistically significantly lower in patients with complete medication reconciliation (20.8% vs 22.4%, $P = 0.63$) and the appropriate reconciliation of beta-blockers (21.9% vs 23.6%, $P = 0.71$) and renin-angiotensin system inhibitors (19.6% vs 20.0%, $P = 0.93$), and nonsignificantly higher with the appropriate reconciliation of antiplatelet agents (23.9% vs 19.9%, $P = 0.40$). Acute hospital visits were statistically significantly lower with the appropriate reconciliation of statins (17.9% vs 31.9%, $P = 0.004$).

In hierarchical multivariable models, complete appropriate medication reconciliation was not associated with acute hospital visits (adjusted odds ratio [AOR], 0.94; 95% confidence interval [CI], 0.63-1.41). For individual medications,

appropriate reconciliation of statins was associated with lower odds of unplanned hospital visits (AOR, 0.47; 95% CI, 0.26-0.85), but there were no statistically significant associations between appropriate reconciliation of antiplatelet agents, beta-blockers, or renin-angiotensin system inhibitors and hospital visits (Table 3). Similarly, the proportion of patients with 30-day unplanned ambulatory visits was not statistically different among patients with complete reconciliation or appropriate reconciliation of individual medications (Table 4). Adjusted analyses were consistent with the unadjusted point estimates and demonstrated no statistically significant associations.

Sensitivity Analysis

Overall, 430 (57.2%) patients had complete cardiovascular medication continuity without considering potential contraindications during hospitalization. Associations between medication continuity and acute hospital and ambulatory visits were similar to the primary analyses.

DISCUSSION

In this study of 752 patients hospitalized for elective noncardiac surgery, we found significant gaps in the appropriate reconciliation of commonly prescribed cardiovascular medications, with inappropriate discontinuation ranging from 18.8% to 52.3% for individual medications. Unplanned postdischarge healthcare utilization was high, with acute hospital visits documented in 21.5% of patients and unplanned ambulatory visits in 16.3% at 30 days after surgery. However, medication reconciliation gaps were not consistently associated with ED visits, hospitalizations, or unplanned ambulatory visits.

Our finding of large gaps in postoperative medication reconciliation is consistent with existing studies of medication reconciliation in surgical patients.[9,10,18] One study found medication discrepancies in 40.2% of postoperative patients receiving usual care and discrepancies judged to have the potential to cause harm (such as the omission of beta-blockers) in 29.9%.[9] Consistent with our findings, this study also found that most postoperative medication discrepancies were omissions in reordering home medications, though at a rate somewhat higher than those seen in medical patients at discharge.[5] While hospitalization by itself increases the risk of unintentional discontinuation of chronic medications,[3] our results, along with existing literature, suggest that the risk for omission of chronic medications is unacceptably high.

We also found significant variation in reconciliation among cardiovascular medications, with appropriate reconciliation occurring least frequently for antiplatelet agents and most frequently for beta-blockers. The low rates of appropriate reconciliation for antiplatelet agents may be attributable to deliberate withholding of antiplatelet therapy in the postoperative period based on clinical assessments of surgical bleeding risk in the absence of active bleeding. Perioperative management of antiplatelet agents for noncardiac surgery remains an unclear and controversial topic, which may also contribute to the variation noted.[19] Conversely, beta-blockers demonstrated high rates of preoperative use (over 80% of patients) and appropriate reconciliation. Both findings are likely attributable in part to the timing of the study, which began prior to the publication of the Perioperative Ischemic Evaluation trial, which more definitively demonstrated the potential harms of perioperative beta-blocker therapy.[20]

Despite a high proportion of patients with discontinuous medications at discharge, we found no associations between the appropriate reconciliation of beta-blockers, renin-angiotensin system inhibitors, and antiplatelet agents and acute hospital or ambulatory visits in the first 30 days after discharge. One explanation for this discrepancy is that, although we focused on cardiovascular medications commonly implicated in acute hospital visits, the vast majority of patients in our study had low perioperative cardiovascular risk as assessed by the RCRI. Previous studies have demonstrated that the benefit of perioperative beta-blocker therapy is predominantly in patients with moderate to high perioperative cardiovascular risk.[21,22] It is possible that the detrimental effects of the discontinuation of chronic cardiovascular medications are more prominent in populations at a higher risk of perioperative cardiovascular complications or that complications will occur later than 30 days after discharge. Similarly, while the benefits of continuation of renin-angiotensin system inhibitors are less clear,[23] few patients in our cohort had a history of congestive heart failure (6.3%) or coronary artery disease (13.0%), 2 conditions in which the impact of perioperative discontinuation of renin-angiotensin inhibitor or beta-blocker therapy would likely be more pronounced.[24,25] An additional explanation for the lack of associations is that, while multiple studies have demonstrated that medication errors are common, the proportion of errors with the potential for harm is much lower, and the proportion that causes actual harm is lower still.[5,26,27] Thus, while we likely captured high-severity medication errors leading to acute hospital or unplanned ambulatory visits, we would not have captured medication errors with lower severity clinical consequences that did not result in medical encounters.

We did find an association between the continuation of statin therapy and reduced ED visits and hospitalizations. This finding is supported by previous studies of patients undergoing noncardiac surgery, including 1 demonstrating an association between immediate postoperative statin therapy and reduced in-hospital mortality[28] and another study demonstrating an association between postoperative statin therapy and reductions in a composite endpoint of 30-day mortality, atrial fibrillation, and nonfatal myocardial infarction.[29] Alternatively, this finding could reflect the effects of unaddressed confounding by factors contributing to statin discontinuation and poor health outcomes leading to acute hospital visits, such as acute elevations in liver enzymes.

Our study has important implications for patients undergoing elective noncardiac surgery and the healthcare providers

caring for them. First, inappropriate omissions of chronic cardiovascular medications at discharge are common; clinicians should increase their general awareness and focus on appropriately reconciling these medications, for even if our results do not connect medication discontinuity to readmissions or unexpected clinical encounters, their impact on patients' understanding of their medications remains a potential concern. Second, the overall high rates of unplanned postdischarge healthcare utilization in this study highlight the need for close postdischarge monitoring of patients undergoing elective surgical procedures and for further research to identify preventable etiologies of postdischarge healthcare utilization in this population. Third, further study is needed to identify specific patient populations and medication classes, in which appropriate reconciliation is associated with patient outcomes that may benefit from more intensive discharge medication reconciliation interventions.

Our study has limitations. First, the majority of patients in this single-center study were at low risk of perioperative cardiovascular events, and our results may not be generalizable to higher-risk patients undergoing elective surgery. Second, discharge reconciliation was based on documentation of medication reconciliation and not on patient-reported medication adherence. In addition, the ability to judge the accuracy of discharge medication reconciliation is in part dependent on the accuracy of the admission medication reconciliation. Thus, although we used preoperative medication regimens documented during preadmission visits to comprehensive preoperative clinics for comparison, discrepancies in these preoperative regimens could have affected our analysis of appropriate discharge reconciliation. Third, inadequate documentation of clinical reasons for discontinuing medications may have led to residual confounding by indication in our observational study. Finally, the outcomes available to us may have been relatively insensitive to other adverse effects of medication discontinuity, such as patient symptoms (eg, angina severity), patient awareness of medications, or work placed on primary care physicians needing to "clean up" erroneous medication lists.

In conclusion, gaps in appropriate discharge reconciliation of chronic cardiovascular medications were common but not consistently associated with postdischarge acute hospital or unplanned ambulatory visits in a relatively low-risk cohort of patients undergoing elective surgery. While appropriate medication reconciliation should always be a priority, further study is needed to identify medication reconciliation approaches associated with postdischarge healthcare utilization and other patient outcomes.

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Antidepressant Use and Depressive Symptoms in Intensive Care Unit Survivors

Sophia Wang, MD[1-3*], Chris Mosher, MD[4], Sujuan Gao, PhD[5], Kayla Kirk, MA[3], Sue Lasiter, PhD, RN[6], Sikandar Khan, DO[7], You Na Kheir, MD[1], Malaz Boustani, MD, MPH[8,9], Babar Khan, MD, MS[7,9]

[1]Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana; [2]Center of Health Innovation and Implementation Science, Center for Translational Science and Innovation, Indianapolis, Indiana; [3]Sandra Eskenazi Center for Brain Care Innovation, Eskenazi Hospital, Indianapolis, Indiana; [4]Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, Indiana; [5]Department of Biostatistics, Indiana University School of Medicine, Indianapolis, Indiana; [6]University of Missouri-Kansas City School of Nursing and Health Studies, Kansas City, Missouri; [7]Division of Pulmonary, Critical Care, Sleep and Occupational Medicine, Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana; [8]Division of Geriatrics and General Internal Medicine, Department of Internal Medicine, Indiana University School of Medicine, Indianapolis, Indiana; [9]IU Center of Aging Research, Regenstrief Institute, Indianapolis, Indiana.

Nearly 30% of intensive care unit (ICU) survivors have depressive symptoms 2-12 months after hospital discharge. We examined the prevalence of depressive symptoms and risk factors for depressive symptoms in 204 patients at their initial evaluation in the Critical Care Recovery Center (CCRC), an ICU survivor clinic based at Eskenazi Hospital in Indianapolis, Indiana. Thirty-two percent (N = 65) of patients had depressive symptoms on initial CCRC visit. For patients who are not on an antidepressant at their initial CCRC visit (N = 135), younger age and lower education level were associated with a higher likelihood of having depressive symptoms. For patients on an antidepressant at their initial CCRC visit (N = 69), younger age and being African American race were associated with a higher likelihood of having depressive symptoms. Future studies will need to confirm these findings and examine new approaches to increase access to depression treatment and test new antidepressant regimens for post-ICU depression. *Journal of Hospital Medicine* 2017;12: 731-734. © 2017 Society of Hospital Medicine

As the number of intensive care unit (ICU) survivors has steadily increased over the past few decades, there is growing awareness of the long-term physical, cognitive, and psychological impairments after ICU hospitalization, collectively known as post–intensive care syndrome (PICS).[1] Systematic reviews based mostly on research studies suggest that the prevalence of depressive symptoms 2-12 months after ICU discharge is nearly 30%.[2-5] Due to the scarcity of established models of care for ICU survivors, there is limited characterization of depressive symptoms and antidepressant regimens in this clinical population. The Critical Care Recovery Center (CCRC) at Eskenazi Hospital is one of the first ICU survivor clinics in the United States and targets a racially diverse, underserved population in the Indianapolis metropolitan area.[6] In this study, we examined whether patients had depressive symptoms at their initial CCRC visit, and whether the risk factors for depressive symptoms differed if they were on an antidepressant at their initial CCRC visit.

METHODS

Referral criteria to the CCRC were 18 years or older, admitted to the Eskenazi ICU, were on mechanical ventilation or delirious for ≥48 hours (major risk factors for the development of PICS), and recommended for follow-up by a critical care physician. The exclusion criterion included was enrollment in hospice or palliative care services. Institutional review board approval was obtained to conduct retrospective analyses of de-identified clinical data. Medical history and medication lists were collected from patients, informal caregivers, and electronic medical records.

Two hundred thirty-three patients were seen in the CCRC from July 2011 to August 2016. Two hundred four patients rated symptoms of depression with either the Patient Health Questionnaire (PHQ-9; N = 99) or Geriatric Depression Scale (GDS-30; N = 105) at their initial visit to the CCRC prior to receiving any treatment at the CCRC. Twenty-nine patients who did not complete depression questionnaires were excluded from the analyses. Patients with PHQ-9 score ≥10 or GDS score ≥20 were categorized as having moderate to severe depressive symptoms.[7,8]

Electronic medical records were reviewed to determine whether patients were on an antidepressant at hospital admission, hospital discharge, and the initial CCRC visit prior to any treatment in the CCRC. Patients who were on a tricyclic antidepressant, selective serotonin reuptake inhibitor, selective serotonin-norepinephrine reuptake inhibitor, noradrenergic and specific serotonergic antidepressant (eg, mirtazapine), or norepinephrine and dopaminergic reuptake inhibitor (eg, bupropion) at any dose were designated as being on an antidepressant. Prescribers of antidepressants included primary care providers, clinical providers during their hospital stay, and various outpatient subspecialists other than those in the CCRC.

***Address for correspondence and reprint requests:** Sophia Wang, MD, 355 W 16th Street, Suite 4800 GH, Room 4250, Indianapolis, IN 46202; Telephone: 317-963-7288; Fax: 317-963-7313; E-mail: sophwang@iupui.edu

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TABLE 1. Demographics and Clinical Characteristics of 204 ICU Survivors Grouped by Depressive Symptoms at Initial CCRC Visit

Characteristics	Overall (N = 204)	Nondepressed (N = 139)	Depressed (N = 65)	*P* Value
Demographics				
Age (years)	52.2 (13.6)	54.7 (13.2)	47.0 (13.3)	<.001
Female, (%)	47.1 (96)	47.5 (66)	46.2 (30)	.86
African American race (%)	43.6 (89)	47.4 (64)	38.5 (25)	.31
Education (years)	11.7 (2.7)	11.8 (2.8)	11.4 (2.5)	.78
Comorbidities				
Alcohol use disorder (current or previous), (%)	33.5 (62)	31.7 (40)	37.3 (22)	.46
Tobacco use disorder (current or previous), (%)	72.6 (146)	70.1 (96)	76.9 (50)	.23
History of depression[a] (%)	48.0 (98)	40.3 (56)	64.6 (42)	<.001
CNS disorder (%)	48.5 (99)	46.0 (64)	53.8 (35)	.30
Cardiac disease (%)	34.8 (71)	39.6 (55)	24.6 (16)	.04
Diabetes mellitus (%)	30.4 (62)	30.9 (43)	29.2 (19)	.81
Hypertension (%)	65.2 (133)	68.3 (95)	58.5 (38)	.17
COPD and other lung disease (%)	47.5 (97)	48.2 (67)	46.2 (30)	.79
Cancer (%)	15.2 (31)	15.8 (22)	13.8 (9)	.71
Hospital Characteristics[b]				
Length of hospitalization (days)	18.7 (17.1)	19.4 (18.1)	17.1 (14.6)	.38
Length of ICU (days)	11.9 (12.9)	12.4 (14.1)	10.9 (9.9)	.48
Delirium during entire hospitalization (%)	59.3 (121)	58.3 (81)	61.5 (40)	.66
Respiratory failure (%)	85.8 (175)	87.8 (122)	81.5 (53)	.24
Antidepressant prescription at hospital admission (%)	30.4 (56)	25.2 (32)	42.1 (24)	.021
Antidepressant prescription at hospital discharge (%)	27.3 (52)	22.1 (29)	39.0 (23)	.016
Initial CCRC Visit Information				
Time between initial visit in CCRC and discharge from the hospital (days)	106.1 (103.09)	105.7 (112.0)	107.1 (79.9)	.93
MMSE (0-30 points)	25.6 (4.9)	25.4 (5.0)	26.1 (4.5)	.41
Antidepressant prescription at initial CCRC visit (%)	33.8 (69)	27.3 (38)	47.7 (31)	.004

[a] History of depression was defined as a diagnosis of depression based on informant report or chart diagnosis of depression.

[b] Hospital stay with sentinel ICU stay resulting in CCRC referral.

NOTE: N = 193-204 except N = 185 for alcohol use, N = 189 for ICU stay, N = 184 for antidepressant at time of hospital admission, and N = 190 for antidepressant at time of hospital discharge. Continuous variables were expressed as average (SD). Dichotomous variables were expressed as % (N). *P* values are from comparisons between the depressed and nondepressed groups. Patients who were on any dose of a tricyclic antidepressant, serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, noradrenergic and specific serotonergic antidepressant (eg, mirtazapine), or norepinephrine and dopaminergic reuptake inhibitor (eg, bupropion) were considered to be on an antidepressant. Antidepressant status was assessed at hospital admission, hospital discharge, and the initial CCRC visit prior to any treatment in the CCRC. Depressive symptoms were defined as patients who indicated moderate to severe depressive symptoms (Geriatric Depression Scale-30 ≥20 or Patient Health Questionnaire-9 ≥10) at the initial CCRC visit prior to treatment in the CCRC. χ^2 testing was used to compare dichotomous outcomes for the 2 groups. Two-tailed Student t tests were used to compare continuous outcomes for the 2 groups. Abbreviations: CCRC, Critical Care Recovery Center; CNS, central nervous disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; MMSE, Mini-Mental State Examination, SD, standard deviation.

We then examined whether the risk factors for depressive symptoms differed if patients were on an antidepressant at their initial CCRC visit. We compared demographic and clinical characteristics between depressed and nondepressed patients not on an antidepressant. We repeated these analyses for those on an antidepressant. Dichotomous outcomes were compared using chi-square testing, and two-way Student t tests for continuous outcomes. Demographic and clinical variables with $P < 0.1$ were included as covariates in a logistic regression model for depressive symptoms separately for those not an antidepressant and those on an antidepressant. History of depression was not included as a covariate because it is highly collinear with post-ICU depression.

RESULTS

Two hundred four ICU survivors in this study reflected a racially diverse and underserved population (monthly income $745.3 ± $931.5). Although most had respiratory failure and/or delirium during their hospital stay, 94.1% (N = 160) mostly lived independently after discharge. Nearly one-third of patients (N = 69) were on at least 1 antidepressant at their initial CCRC visit. Of these 69 patients, 60.9% (N = 42) had an antidepressant prescription on hospital admission, and 60.9% (N = 42) had an antidepressant prescription on hospital discharge.

We first compared the demographic and clinical characteristics of patients with and without depressive symptoms at their initial CCRC visit. Patients with depressive symptoms were younger, less likely to have cardiac disease, more likely to have a history of depression, more likely to have been prescribed an antidepressant on hospital admission, more likely to be prescribed an antidepressant on hospital discharge, and more likely to be on an antidepressant at their initial CCRC visit (Table 1).

We then compared whether demographic and clinical characteristics of patients with and without depressive symptoms differed by antidepressant status at their initial CCRC visit. Patients with depressive symptoms who were not on

antidepressants (N = 135) were younger, had fewer years of education, were more likely to have a history of depression, were less likely to have a cardiac history, and were less likely to have hypertension (Supplementary Table 1). Multivariate logistic regression showed that only younger age (odds ratio [OR] = 0.96 per year, $P = 0.023$) and lower education (OR = 0.81, $P = 0.014$) remained significantly associated with depressive symptoms (Table 2).

Patients with depressive symptoms on an antidepressant (n = 65) were younger and more likely to be African American (borderline significance; Supplementary Table 2). Multivariate logistic regression showed that both younger age (OR = 0.92 per year, $P = 0.003$) and African American race (OR = 4.3, $P = 0.024$) remained significantly associated with depressive symptoms (Table 2).

TABLE 2. Risk Factors for Depressive Symptoms Based on Antidepressant Status[a]

Not on an Antidepressant (N = 135)		On an Antidepressant (N = 69)	
Characteristics	OR (95% CI)	Characteristics	OR (95% CI)
Age (per year)	0.96 (0.93-0.99)	Age (per year)	0.92 (0.87-0.97)
Education level	0.81 (0.68-0.96)	African American race	4.30 (1.21-15.28)
Cardiac history	0.64 (0.21-1.98)		
Hypertension	0.73 (0.27-1.96)		

[a]Antidepressant status was assessed at the initial CCRC visit prior to treatment in CCRC.

NOTE: OR and 95% CI were calculated using logistic regression models. Abbreviations: CCRC, Critical Care Recovery Center; CI, confidence interval; OR, odds ratio.

DISCUSSION

Our study demonstrated that about one-third of our ICU survivor clinical cohort had untreated or inadequately treated depressive symptoms at their CCRC initial visit. Many patients with depressive symptoms had a history of depression and/or antidepressant prescription on hospital admission. This suggests that pre-ICU depression is a major contributor to post-ICU depression. These findings are consistent with the results of a large retrospective analysis of Danish ICU survivors that found that patients were more likely to have premorbid psychiatric diagnoses, compared with the general population.[9] Another ICU survivor research study that excluded patients who were on antidepressants prior to ICU hospitalization found that 49% of these patients were on an antidepressant after their ICU stay.[10] Our much lower rate of patients on an antidepressant after their ICU stay may reflect the differences between patient populations, differences in healthcare systems, and differences in clinician prescribing practices.

Younger age was associated with a higher likelihood of depressive symptoms independent of antidepressant status. Findings about the relationship between age and post-ICU depression have varied. The Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors group found that older age was associated with more depressive symptoms at 12 months postdischarge.[11] On the other hand, a systematic review of post-ICU depression did not find any relationship between age and post-ICU depression.[2,3] These differences may be due in part to demographic variations in cohorts.

Our logistic regression models suggest that there may also be different risk factors in patients who had untreated vs inadequately treated depressive symptoms. Patients who were not on an antidepressant at their initial CCRC visit were more likely to have a lower level of education. This is consistent with the Medical Expenditure Panel Surveys study, which showed that adults with less than a high school education were less likely to receive depression treatment.[12] In patients who were on antidepressants at their initial CCRC visit, African Americans were more likely to have depressive symptoms. Possible reasons may include differences in receiving guideline-concordant antidepressant medication treatment, access to mental health subspecialty services, higher prevalence of treatment refractory depression, and differences in responses to antidepressant treatments.[13,14]

Strengths of our study include detailed characterization for a fairly large ICU survivor clinic population and a racially diverse cohort. To the best of our knowledge, our study is also the first to examine whether there may be different risk factors for depressive symptoms based on antidepressant status. Limitations include the lack of information about nonpharmacologic antidepressant treatment and the inability to assess whether noncompliance, insufficient dose, or insufficient time on antidepressants contributed to inadequate antidepressant treatment. Antidepressants may have also been prescribed for other purposes such as smoking cessation, neuropathic pain, and migraine headaches. However, because 72.4% of patients on antidepressants had a history of depression, it is likely that most of them were on antidepressants to treat depression.

Other limitations include potential biases in our clinical cohort. Over the last 5 years, the CCRC has provided care to more than 200 ICU survivors. With 1100 mechanically ventilated admissions per year, only 1.8% of survivors are seen. The referral criteria for the CCRC is a major source of selection bias, which likely overrepresents PICS. Because patients are seen in the CCRC about 3 months after hospital discharge, there is also informant censoring due to death. Physically sicker survivors in nursing home facilities were less likely to be included. Finally, the small cohort size may have resulted in an underpowered study.

Future studies will need to confirm our findings about the high prevalence of post-ICU depression and different responses to antidepressant medications by certain groups. Pre-ICU depression, lack of antidepressant treatment, and inadequate antidepressant treatment are major causes of post-ICU depression. Currently, the CCRC offers pharmacotherapy, problem-solving therapy, or referral to mental health specialists to treat patients with depressive symptoms. ICU survivor clinics, such as the CCRC, may become important settings that allow for increased access to depression treatment for those at higher risk for post-ICU depression as

well as the testing of new antidepressant regimens for those with inadequately treated depression.

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Magnitude of Potentially Inappropriate Thrombophilia Testing in the Inpatient Hospital Setting

Eric Mou, MD[1*], Henry Kwang, MD[1], Jason Hom, MD[1], Lisa Shieh, MD[1], Andre Kumar, MD[1], Ilana Richman, MD[1], Caroline Berube, MD[2]

[1]Department of Medicine, Stanford University, Stanford, California; [2]Division of Hematology, Stanford University, Stanford, California.

Laboratory costs of thrombophilia testing exceed an estimated $650 million (in US dollars) annually. Quantifying the prevalence and financial impact of potentially inappropriate testing in the inpatient hospital setting represents an integral component of the effort to reduce healthcare expenditures. We conducted a retrospective analysis of our electronic medical record to evaluate 2 years' worth of inpatient thrombophilia testing measured against preformulated appropriateness criteria. Cost data were obtained from the Centers for Medicare and Medicaid Services 2016 Clinical Laboratory Fee Schedule. Of the 1817 orders analyzed, 777 (42.7%) were potentially inappropriate, with an associated cost of $40,422. The tests most frequently inappropriately ordered were Factor V Leiden, prothrombin gene mutation, protein C and S activity levels, antithrombin activity levels, and the lupus anticoagulant. Potentially inappropriate thrombophilia testing is common and costly. These data demonstrate a need for institution-wide changes in order to reduce unnecessary expenditures and improve patient care. *Journal of Hospital Medicine.* 2017;12:735-738. © 2017 Society of Hospital Medicine

Venous thromboembolism (VTE) affects more than 1 million patients and costs the US healthcare system more than $1.5 billion annually.[1] Inherited and acquired thrombophilias have been perceived as important risk factors in assessing the risk of VTE recurrence and guiding the duration of anticoagulation.

Thrombophilias increase the risk of a first thrombotic event, but existing data have failed to demonstrate the usefulness of routine thrombophilia screening on subsequent management.[2,3] Moreover, thrombophilia testing ordered in the context of an inpatient hospitalization is limited by confounding factors, especially during an acute thrombotic event or in the setting of concurrent anticoagulation.[4]

Recognizing the costliness of routine thrombophilia testing, The American Society of Hematology introduced its Choosing Wisely campaign in 2013 in an effort to reduce test ordering in the setting of provoked VTEs with a major transient risk factor.[5] In order to define current practice behavior at our institution, we conducted a retrospective study to determine the magnitude and financial impact of potentially inappropriate thrombophilia testing in the inpatient setting.

METHODS

We performed a retrospective analysis of thrombophilia testing across all inpatient services at a large, quaternary-care academic institution over a 2-year period. Electronic medical record data containing all thrombophilia tests ordered on inpatients from June 2013 to June 2015 were obtained. This study was exempt from institutional review board approval.

Inclusion criteria included any inpatient for which thrombophilia testing occurred. Patients were excluded if testing was ordered in the absence of VTE or arterial thrombosis or if it was ordered as part of a work-up for another medical condition (see Supplementary Material).

Thrombophilia testing was defined as any of the following: inherited thrombophilias (Factor V Leiden or prothrombin 20210 gene mutations, antithrombin, or protein C or S activity levels) or acquired thrombophilias (lupus anticoagulant [Testing refers to the activated partial thromboplastin time lupus assay.], beta-2 glycoprotein 1 immunoglobulins M and G, anticardiolipin immunoglobulins M and G, dilute Russell's viper venom time, or JAK2 V617F mutations).

Extracted data included patient age, sex, type of thrombophilia test ordered, ordering primary service, admission diagnosis, and objective confirmation of thrombotic events. The indication for test ordering was determined via medical record review of the patient's corresponding hospitalization. Each test was evaluated in the context of the patient's presenting history, hospital course, active medications, accompanying laboratory and radiographic studies, and consultant recommendations to arrive at a conclusion regarding both the test's reason for ordering and whether its indication was "inappropriate," "appropriate," or "equivocal." Cost data were obtained through the Centers for Medicare & Medicaid Services (CMS) Clinical Laboratory Fee Schedule for 2016 (see Supplementary Material).[6]

The criteria for defining test appropriateness were formulated by utilizing a combination of major society guidelines and literature review.[5,7-10] The criteria placed emphasis upon the ordered tests' clinical relevance and reliability and were subsequently reviewed by a senior hematologist with specific expertise in thrombosis (see Supplementary Material).

***Address for correspondence and reprint requests:** Eric Mou, MD, 300 Pasteur Drive, Stanford, CA 94304; Telephone: 515-771-9639; Fax: 650-725-8381; E-mail: emou@stanford.edu

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TABLE. General Testing Data Characteristics

Unique Patients	Number of Tests[a]	Number of Inappropriate Tests (%)	Cost of Inappropriate Ordering (USD)
299	1817	777 (42.7)	$40,422
Site of thrombosis			
DVT	424	157 (37.0)	$8517
PE	500	251 (50.2)	$13,758
CVA	458	158 (34.5)	$7343
Arterial thrombosis (PVD + other end organs)	276	130 (47.1)	$6846
Cerebral venous thrombosis	104	50 (48.1)	$2412
Splanchnic vein thrombosis	88	41 (46.6)	$2127
Other	57	20 (35.1)	$1099

[a]Some tests were ordered in the setting of synchronous thrombotic diagnoses, resulting in the sum of testing by site of thrombosis exceeding the total number of tests.
NOTE: Abbreviations: CVA, cerebrovascular accident; DVT, deep venous thrombosis; PE, pulmonary embolism; PVD, peripheral vascular disease; USD, US dollars.

Two internal medicine resident physician data reviewers independently evaluated the ordered tests. To ensure consistency between reviewers, a sample of identical test orders was compared for concordance, and a Cohen's kappa coefficient was calculated. For purposes of analysis, equivocal orders were included under the appropriate category, as this study focused on the quantification of potentially inappropriate ordering practices. Pearson chi-square testing was performed in order to compare ordering practices between services using Stata.[11]

RESULTS

In total, we reviewed 2179 individual tests, of which 362 (16.6%) were excluded. The remaining 1817 tests involved 299 patients across 26 primary specialties. Fifty-two (2.9% of orders) were ultimately deemed equivocal. The Table illustrates the overall proportion and cost of inappropriate test ordering as well as testing characteristics of the most commonly encountered thrombotic diagnoses. The Figure illustrates the proportion of potentially inappropriate test ordering with its associated cost by test type.

Orders for Factor V Leiden, prothrombin 20210, and protein C and S activity levels were most commonly deemed inappropriate due to the test results' failure to alter clinical management (97.3%, 99.2%, 99.4% of their inappropriate orders, respectively). Antithrombin testing (59.4%) was deemed inappropriate most commonly in the setting of acute thrombosis. The lupus anticoagulant (82.8%) was inappropriately ordered most frequently in the setting of concurrent anticoagulation.

Ordering practices were then compared between nonteaching and teaching inpatient general medicine services. We observed a higher proportion of inappropriate tests ordered by the nonteaching services as compared to the teaching services (120 of 173 orders [69.4%] versus 125 of 320 [39.1%], respectively; $P < 0.001$).

The interreviewer kappa coefficient was 0.82 ($P < 0.0001$).

DISCUSSION

This retrospective analysis represents one of the largest examinations of inpatient thrombophilia testing practices to date. Our results illustrate the high prevalence and significant financial impact of potentially inappropriate thrombophilia testing conducted in the inpatient setting. The data confirm that, per our defined criteria, more than 90% of inherited thrombophilia testing was potentially inappropriate while the majority of acquired thrombophilia testing was appropriate, with the exception of the lupus anticoagulant.

Even when appropriately ordered, studies suggest that positive thrombophilia screening results fail to impact outcomes in most patients with VTE. In an effort to evaluate positive results' potential to provide a basis from which to extend the duration of anticoagulation, and therefore reduce the risk of a recurrent VTE, a case-control analysis was performed on a series of patients with a first-VTE event (Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis [MEGA] study).[3] In examining the odds ratio (OR) for recurrence between patients who did or did not undergo testing for Factor V Leiden, antithrombin, or protein C or S activity, the data failed to show an impact of testing on the risk of VTE recurrence (OR 1.2; confidence interval, 0.8-1.8). In fact, decision making has increasingly relied on patients' clinical characteristics rather than thrombophilia test results to guide anticoagulation duration after incident VTEs. A 2017 study illustrated that when using a clinical decision rule (Clinical Decision Rule Validation Study to Predict Low Recurrent Risk in Patients With Unprovoked Venous Thromboembolism [REVERSE criteria]) in patients with a first, unprovoked VTE, routine thrombophilia screening added little to determining the need for prolonged anticoagulation.[12] These findings support the limited clinical utility of current test ordering practices for the prediction and management of recurrent venous thrombosis.

Regarding the acquired thrombophilias, antiphospholipid antibody testing was predominantly ordered in a justified manner, which is consistent with the notion that test results could affect clinical management, such as anticoagulation duration or choice of anticoagulant.[13] However, the validity of lupus anticoagulant testing was limited by the frequency of patients on concurrent anticoagulation.

Financially, the cumulative cost associated with inappropriate ordering was substantial, regardless of the thrombotic

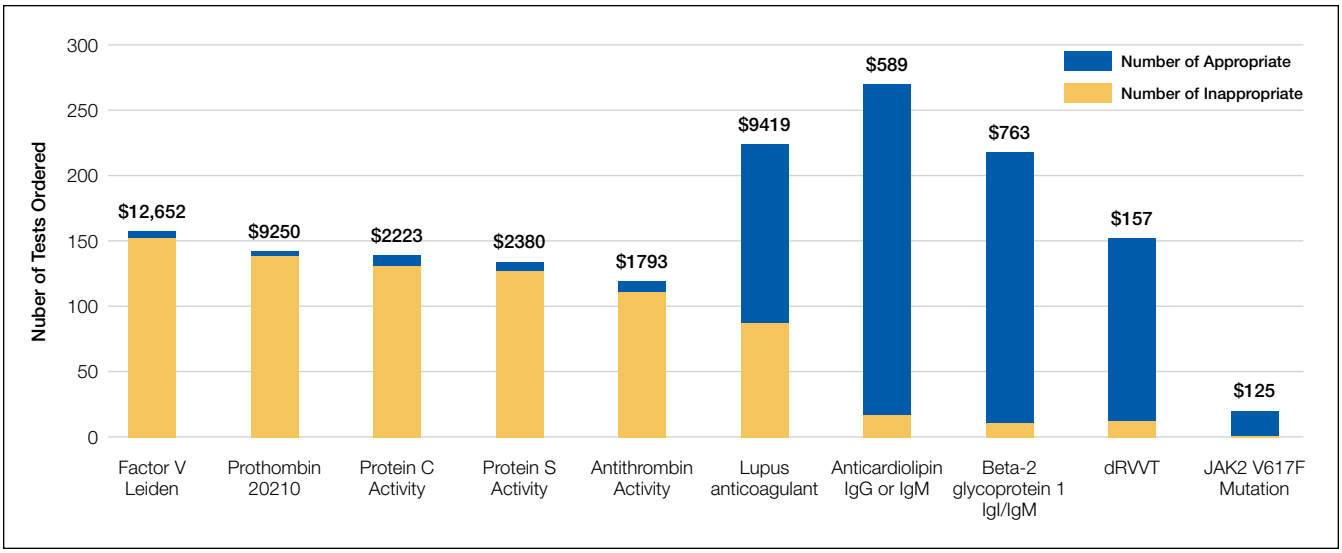

FIG. Proportion of Inappropriate Test Ordering with Associated Cost, by Test Type. Each bar represents the total number of orders and the proportion of inappropriate/appropriate orders for each thrombophilia test. The cost figures above each bar show the total cost of the corresponding test's inappropriate orders, according to the 2016 Centers for Medicare and Medicaid Services (CMS) Clinical Laboratory Fee Schedule.

event in question. Moreover, our calculated costs are derived from CMS reimbursement rates and likely underestimate the true financial impact of errant testing given that commercial laboratories frequently charge at rates several-fold higher. On a national scale, prior analyses have suggested that the annual cost of thrombophilia testing, based on typical commercial rates, ranges from $300 million to $672 million.[14]

Researchers in prior studies have similarly examined the frequency of inappropriate thrombophilia testing and methods to reduce it. Researchers in a 2014 study demonstrated initially high rates of inappropriate inherited thrombophilia testing, and then showed marked reductions in testing and cost savings across multiple specialties following the introduction of a flowchart on a preprinted order form.[15] Our findings provide motivation to perform similar endeavors.

The proportional difference of inappropriate ordering observed between nonteaching- and teaching-medicine services indicates a potential role for educational interventions. We recently completed a series of lectures on high-value thrombophilia ordering for residents and are actively analyzing its impact on subsequent ordering practices. We are also piloting an electronic best practice advisory for thrombophilia test ordering. Though the advisory may be overridden, providers are asked to provide justification for doing so on a voluntary basis. We plan to evaluate its effect on our findings reported in this study.

We acknowledge that our exclusion criteria resulted in the omission of testing across a spectrum of nonthrombotic clinical conditions, raising the question of selection bias. Because there are no established guidelines to determine the appropriateness of testing in these scenarios, we chose to limit the analysis of errant ordering to the context of thrombotic events. Other limitations of this study include the analysis of equivocal orders as appropriate. However, because equivocal ordering represented less than 3% of all analyzed orders, including these as inappropriate would not have significantly altered our findings.

CONCLUSIONS

A review of thrombophilia testing practices at our institution demonstrated that inappropriate testing in the inpatient setting is a frequent phenomenon associated with a significant financial impact. This effect was more pronounced in inherited versus acquired thrombophilia testing. Testing was frequently confounded and often failed to impact patients' short- or long-term clinical management, regardless of the result.

These findings serve as a strong impetus to reduce the burden of routine thrombophilia testing during hospital admissions. Our data demonstrate a need for institution-wide changes such as implementing best practice advisories, introducing ordering restrictions, and conducting educational interventions in order to reduce unnecessary expenditures and improve patient care.

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Blood Products Provided to Patients Receiving Futile Critical Care

Thanh H. Neville, MD, MSHS[1*], Alyssa Ziman, MD[2], Neil S. Wenger, MD, MPH[3,4,5]

[1]Department of Medicine, Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; [2]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; [3]University of California Health Ethics Center, Los Angeles, California; [4]Deparment of Medicine, Division of General Internal Medicine and Health Services Research, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; [5]RAND Health, Santa Monica, California.

The number of hospitalized patients receiving treatment perceived to be futile is not insignificant. Blood products are valuable resources that are donated to help others in need. We aimed to quantify the amount of blood transfused into patients who were receiving treatment that the critical care physician treating them perceived to be futile. During a 3-month period, critical care physicians in 5 adult intensive care units completed a daily questionnaire to identify patients perceived as receiving futile treatment. Of 1136 critically ill patients, physicians assessed 123 patients (11%) as receiving futile treatment. Fifty-nine (48%) of the 123 patients received blood products after they were assessed to be receiving futile treatment: 242 units of packed red blood cells (PRBCs) (7.6% of all PRBC units transfused into critical care patients during the 3-month study period); 161 (9.9%) units of plasma, 137 (12.1%) units of platelets, and 21 (10.5%) units of cryoprecipitate. Explicit guidelines on the use of blood products should be developed to ensure that the use of this precious resource achieves meaningful goals. *Journal of Hospital Medicine* 2017;12:739-742. © 2017 Society of Hospital Medicine

Critical care physicians frequently find themselves providing care that they find to be futile or inappropriate for hospitalized critically ill patients. A survey of physicians found that 87% felt that "futile" treatment was provided in their intensive care unit (ICU) in the past year.[1] In a single-day cross-sectional study, 27% of ICU clinicians reported providing inappropriate care to at least 1 patient, most of which was excessive.[2] In a 3-month study, 11% of all ICU patients were perceived by their physician as receiving futile treatment at some point during their ICU hospitalization.[3] Given that more than 1 in 5 decedents die after an ICU stay during a terminal admission, there is increasing scrutiny of the ICU as a setting where potentially inappropriate resource-intensive treatment is provided.[4-6] Blood is an especially valuable resource, not only because it exists in finite supply (and is sometimes in shortage) but also because it is donated in ways that arguably create special stewardship expectations and responsibilities for those trusted to make decisions about its use. The amount of blood products used for patients who are perceived to be receiving inappropriate critical care has not been quantified.

Blood transfusion is the most frequently performed inpatient procedure, occurring in more than 10% of hospital admissions that involve a procedure.[7] When used appropriately, the transfusion of blood products can be lifesaving; however, studies show that some transfused blood might not be needed and efforts are afoot to improve the match between transfusion and transfusion need.[8,9] These efforts largely focus on generating guidelines based on physiologic benefit and aim mainly at promoting a restrictive transfusion protocol by avoiding blood product use for patients who will likely do well even without transfusion.[8,10-12] The guiding principle behind efforts to improve the stewardship of scarce blood products is that they should only be used if they will make a difference in patient outcomes. Unlike prior studies, the goal of this study is to quantify the amount of blood products administered to patients who would do poorly with or without receipt of blood products, that is, patients perceived by their physicians as receiving futile critical care.

MATERIALS AND METHODS

Based on a focus group discussion with physicians who cared for critically ill patients, a questionnaire was developed to identify patients perceived as receiving futile critical care. Details of the definition of futile treatment and the core data collection are described in detail elsewhere.[3]

For each ICU patient under the physician's care, the attending physician completed a daily questionnaire asking whether the patient was receiving futile treatment, probably futile treatment, or nonfutile treatment. These surveys were administered every day from December 15, 2011, through March 15, 2012, to each critical care specialist providing care in 5 ICUs (medical ICU, neurocritical care ICU, cardiac care unit, cardiothoracic ICU, and a mixed medical-surgical ICU) in 1 academic health system. All clinicians provided informed consent.

Patients were categorized into the following 3 groups: pa-

***Address for correspondence and reprint requests:** Thanh H. Neville, MD, MSHS, Department of Medicine, Division of Pulmonary and Critical Care Medicine, Box 951690, 37-131 CHS, Los Angeles, CA 90095-1690; Telephone: 310-825-859; Fax 310-206-8622; E-mail: tneville@mednet.ucla.edu

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TABLE. Quantity of Blood Products Administered to Patients Who Were Assessed during the 3-Month Study Period

Blood Product	Units Transfused During 3-Month Period	Units Transfused after Patient Assessed as Receiving *Probably Futile* Treatment[a]	Units Transfused after Patient Assessed as Receiving *Futile* Treatment
Packed red blood cells	3179	347 (10.9%)	242 (7.6%)
Fresh frozen plasma	1624	243 (15%)	161 (9.9%)
Platelets	1130	189 (16.7%)	137 (12.1%)
Cryoprecipitate	201	24 (11.9%)	21 (10.5%)

[a]Because patients usually were assessed as receiving probably futile treatment before being assessed as receiving futile treatment, blood products received after a patient was assessed as receiving futile treatment (column 3) is a subset of blood products received after a patient was assessed as receiving futile treatment (column 2).

NOTE: Percentages in parenthesis refer to proportion of product usage by patients who were perceived as receiving futile critical care.

tients for whom treatment was never perceived as futile; patients with at least 1 assessment that treatment was probably futile, but no futile treatment assessments; and patients who had at least 1 assessment of futile treatment. Hospital and 6-month mortality was abstracted for all patients.

The Division of Transfusion Medicine provided a database of all adult patients during the 3-month study period who received a transfusion of packed red blood cells (PRBCs), apheresis platelets, plasma, or cryoprecipitate (5 unit prepooled units). This database was merged with the daily assessments of the appropriateness of critical care. To determine the proportion of blood products that was utilized for patients receiving inappropriate treatment, we tallied the blood products infused to these patients after the day the patient was assessed as receiving probably inappropriate or inappropriate treatment. The denominator was the total amount of blood products used by all assessed patients during the 3-month study period.

This study was approved by the University of California Los Angeles Institutional Review Board (IRB# 11-002942-CR-00004).

RESULTS

During the 3-month study period, 36 critical care clinicians in 5 ICUs provided care to 1193 adult patients. After excluding boarders in the ICUs and missed and invalid assessments, 6916 assessments were made on 1136 patients. Of these 1136 patients, 98 (8.6%) patients received probably futile treatment and 123 (11%) patients received futile treatment according to the physicians caring for them.

For patients who were never rated as receiving futile treatment, the in-hospital mortality was 4.6% and the 6-month mortality was 7.3%. On the contrary, 68% of the patients who were perceived to receive futile ICU treatment died before hospital discharge and 85% died within 6 months; survivors remained in severely compromised health states.[3]

Of 1136 patients, 595 (52.4%) patients received at least 1 unit of blood product infusion during the 3-month period. These patients received 3179 units of PRBCs, 1624 units of plasma, 1130 units of platelets, and 201 units of cryoprecipitate. Of the 123 patients assessed as receiving futile critical care, 59 (48.0%) patients received blood product infusions during the study period after they were assessed as receiving futile treatment. Eighteen of these patients (30.5%) were in surgical ICUs and 41 (69.5%) were in medical and neuro-ICUs. After being classified as receiving futile critical care, these patients were transfused 242 units of PRBCs, which was 7.6% of the PRBCs received by the study cohort. The mean number of blood products (PRBC, fresh frozen plasma, platelet, or cryoprecipitate) transfused per patient was 9.8 units (range 1-80) with 56% of patients receiving less than 4 units. Patients assessed as receiving futile treatment also received 161 (9.9%) units of plasma, 137 (12.1%) units of platelets, and 21 (10.5%) units of cryoprecipitate (Table, which also shows the amount of blood utilized after the patient had an assessment of probably futile treatment). Patients who received blood products after they were assessed as receiving futile treatment had a 6-month mortality of 95%. The figure shows the derivation of the study sample, blood products received and patient outcomes.

DISCUSSION

Blood and blood products are donated resources. These biological products are altruistically given with the expectation that they will be used to benefit others.[13] It is the clinicians' responsibility to use these precious gifts to achieve the goals of medicine, which include curing, preserving function, and preventing clinical deterioration that has meaning to the patient. Our study shows that a small, but not insignificant, proportion of these donated resources are provided to hospitalized patients who are perceived as receiving futile critical care. That means that these transfusions are used as part of the critical care interventions that prolong the dying process and achieve outcomes, such as existence in coma, which few, if any, patients would desire. However, it should be noted that some of the health states preserved, such as neurological devastation or multi-organ failure with an inability to survive outside an ICU, were likely desired by patients' families and might even have been desired by patients themselves. Whether blood donors would wish to donate

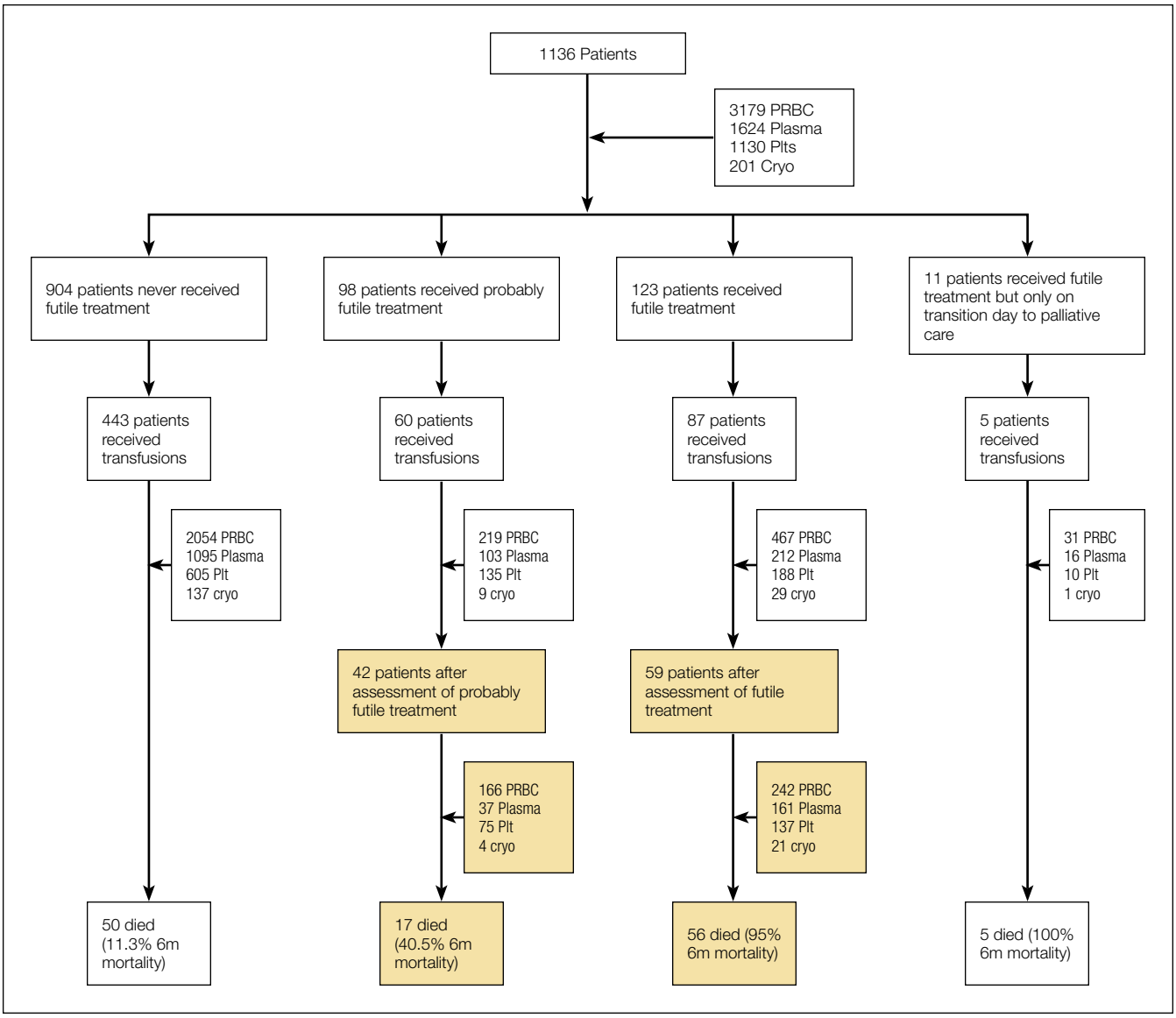

FIG. Derivation of the study sample, the blood products received and patient outcomes. Shaded boxes show transfusions that occurred after a patient was assessed as receiving probably futile or futile treatment. NOTE: Abbreviations: cryo, cryoprecipitate; m, month; Plt, platelet; PRBC, packed red blood cells

blood to preserve life in such compromised health states is testable. This proportion of blood provided to ICU patients perceived as receiving futile treatment (7.6%) is similar to or greater than that lost due to wastage, which ranges from 0.1% to 6.7%.[14] While the loss of this small proportion of blood products due to expiration or procedural issues is probably unavoidable, but should be minimized as much as possible, the provision of blood products to patients receiving futile critical care is under the control of the healthcare team. This raises the question of how altruistic blood donors would feel about donating if they were aware that 1 of every 13 units transfused in the ICU would be given to a patient that the physician feels will not benefit. In turn, it raises the question of whether the physician should refrain from using these blood products for patients who will not benefit in accordance with principles of evidence-based medicine, in order to ensure their availability for patients that will benefit.

This study has several limitations. Family/patient perspectives were not included in the assessment of futile treatment. It should also be recognized that the percentage of blood products provided to patients receiving inappropriate critical care is likely an underestimate as only blood product use during the 3-month study period was included, as many of these patients were admitted to the ICU prior the study period, and/or remained in the ICU or hospital after this window.

CONCLUSIONS

Similar to other treatments provided to patients who are perceived to receive futile critical care, blood products represent a healthcare resource that has the potential to be used

without achieving the goals of medicine. But unlike many other medical treatments, the ability to maintain an adequate blood supply for transfusion relies on altruistic blood donors, individuals who are simply motivated by a desire to achieve a healthcare good.[13] Explicit guidelines on the use of blood products should be developed to ensure that the use of this precious resource achieves meaningful goals. These goals need to be transparently defined such that a physician's decision to not transfuse is expected as part of evidence-based medicine. Empiric research, educational interventions, and clearly delineated conflict-resolution processes may improve clinicians' ability to handle these difficult cases.[15]

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Internal Medicine Resident Engagement with a Laboratory Utilization Dashboard: Mixed Methods Study

Gregory Kurtzman, BA[1,2,3], Jessica Dine, MD, MS[4], Andrew Epstein, PhD[1,2,5], Yevgeniy Gitelman MD[3,5], Damien Leri, MS Ed, MPH[3], Mitesh S. Patel, MD, MBA, MS[1,2,3,5], Kira Ryskina, MD, MS[1,2]*

[1]Division of General Internal Medicine, University of Pennsylvania, Philadelphia, Pennsylvania; [2]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania; [3]Penn Medicine Center for Health Care Innovation, University of Pennsylvania Health System, Philadelphia, Pennsylvania; [4]Division of Pulmonary and Critical Care, University of Pennsylvania, Philadelphia, Pennsylvania; [5]Corporal Michael J. Crescenz VA Medical Center, Philadelphia, Pennsylvania.

The objective of this study was to measure internal medicine resident engagement with an electronic medical record-based dashboard providing feedback on their use of routine laboratory tests relative to service averages. From January 2016 to June 2016, residents were e-mailed a snapshot of their personalized dashboard, a link to the online dashboard, and text summarizing the resident and service utilization averages. We measured resident engagement using e-mail read-receipts and web-based tracking. We also conducted 3 hour-long focus groups with residents. Using grounded theory approach, the transcripts were analyzed for common themes focusing on barriers and facilitators of dashboard use. Among 80 residents, 74% opened the e-mail containing a link to the dashboard and 21% accessed the dashboard itself. We did not observe a statistically significant difference in routine laboratory ordering by dashboard use, although residents who opened the link to the dashboard ordered 0.26 fewer labs per doctor-patient-day than those who did not (95% confidence interval, –0.77 to 0.25; $P = 0.31$). While they raised several concerns, focus group participants had positive attitudes toward receiving individualized feedback delivered in real time. *Journal of Hospital Medicine* 2017;12:743-746. © 2017 Society of Hospital Medicine

Recent efforts to reduce waste and overuse in healthcare include reforms, such as merit-based physician reimbursement for efficient resource use[1] and the inclusion of cost-effective care as a competency for physician trainees.[2] Focusing on resource use in physician training and reimbursement presumes that teaching and feedback about utilization can alter physician behavior. Early studies of social comparison feedback observed considerable variation in effectiveness, depending on the behavior targeted and how feedback was provided to physicians.[3-5] The widespread adoption of electronic medical record (EMR) software enables the design of feedback interventions that provide continuous feedback in real-time via EMR-based practice dashboards. Currently, little is known about physician engagement with practice dashboards and, in particular, about trainee engagement with dashboards aimed to improve cost-effective care.

To inform future efforts in using social comparison feedback to teach cost-effective care in residency, we measured internal medicine resident engagement with an EMR-based utilization dashboard that provides feedback on their use of routine laboratory tests on an inpatient medicine service. Routine labs are often overused in the inpatient setting. In fact, one study reported that 68% of laboratory tests ordered in an academic hospital did not contribute to improving patient outcomes.[6] To understand resident perceptions of the dashboards and identify barriers to their use, we conducted a mixed methods study tracking resident utilization of the dashboard over time and collecting qualitative data from 3 focus groups about resident attitudes toward the dashboards.

METHODS

From January 2016 to June 2016, resident-specific rates of routine lab orders (eg, complete blood count, basic metabolic panel, complete metabolic panel, liver function panel, and common coagulation tests) were synthesized continuously in a web-based dashboard. Laboratory orders could be placed either individually on a day-to-day basis or ordered on a recurrent basis (eg, daily morning labs ordered on admission). The dashboard contained an interactive graph, which plotted the average number of labs per patient-day ordered by each resident over the past week, along with an overall graph for all services for comparison (Appendix Figure). Residents could click on an individual day on the graph to review the labs they ordered for each patient. The dashboard also allowed the user to look up each patient's medical record to obtain more detailed information.

All residents received an e-mail describing the study, including the purpose of the intervention, basic description of the feedback intervention (dashboard and e-mail), potential risks and benefits, duration and scope of data collection, and contact information of the principal investigator. One hundred and ninety-eight resident-blocks on 6 general medicine services at the Hospital of the University of Pennsylvania were cluster-randomized with an equal probability to 1 of 2

***Address for correspondence and reprint requests:** Kira Ryskina, MD, 12-30 12th Floor, Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104; Telephone: 215-898-3935; E-mail: ryskina@mail.med.upenn.edu

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TABLE 1. Odds of Accessing the Online Dashboard by Resident Characteristics

Resident Characteristic	Odds Ratio	95% Confidence Interval	*P* Values
Absolute difference of 1 standard deviation of labs per patient-day from service average[a]	1.48	1.01-2.17	.047
Ordering more tests than service average[b]	1.11	0.45-2.73	.83
PGY2 or 3 (reference = PGY1)	1.06	0.37-3.03	.91
First occurrence of intervention	1.38	0.31-6.10	.68
Weeks since start of intervention	0.92	0.80-1.06	.23
Whether other members of team opened the link	1.10	0.32-3.72	.88

[a] Absolute difference of 1 standard deviation of labs per patient-day from service average means that the resident's ordering rate was 1 standard deviation higher or lower than the service average.

[b] Ordering more tests than service average means that the resident's ordering rate was higher than the service average.

NOTE: Abbreviation: PGY, postgraduate year.

arms: (1) those e-mailed a snapshot of the personalized dashboard, a link to the online dashboard, and text containing resident and service utilization averages, and (2) those who did not receive the feedback intervention. Postgraduate year (PGY) 1 residents were attributed only orders by that resident. PGY2 and PGY3 residents were attributed orders for all patients assigned to the resident's team.

The initial e-mails were timed to arrive in the middle of each resident's 2-week service to allow for a baseline and follow-up period. The e-mail contained an attachment of a snapshot of the personalized graphic dashboard (Appendix Figure), a link to the online dashboard, and a few sentences summarizing the resident utilization average compared to the general medicine service overall, for the same time interval. They were followed by a reminder e-mail 24 hours later containing only the link to the report card. We measured resident engagement with the utilization dashboard by using e-mail read-receipts and a web-based tracking platform that recorded when the dashboard was opened and who logged on.

Following completion of the intervention, 3-hour-long focus groups were conducted with residents. These focus groups were guided with prescripted questions to prompt discussion on the advantages and drawbacks of the study intervention and the usage of dashboards in general. These sessions were digitally recorded and transcribed. The transcripts were reviewed by 2 authors (KR and GK) and analyzed to identify common themes by using a grounded theory approach.[7] First, the transcripts were reviewed independently by each author, who each generated a broad list of themes across 3 domains: dashboard usability, barriers to use, and suggestions for the future. Next, the codebook was refined through an iterative series of discussions and transcript review, resulting in a unified codebook. Lastly, all transcripts were reviewed by using the final codebook definitions, resulting in a list of exemplary quotes and suggestions.

The study was approved by the University of Pennsylvania Institutional Review Board and registered on clinicaltrials.gov (NCT02330289).

RESULTS

Eighty unique residents participated in the intervention, including 51 PGY1s (64%) and 29 PGY2- or PGY3-level (36%) residents. Of these, 19/80 (24%) physicians participated more than once. 74% of participants opened the e-mail and 21% opened the link to the dashboard. The average elapsed time from receiving the initial e-mail to logging into the dashboard was 28.5 hours (standard deviation [SD] = 25.7, median = 25.5, interquartile range [IQR] = 40.5). On average, residents deviated from the service mean by 0.54 laboratory test orders (SD = 0.49, median = 0.40, IQR = 0.60). The mean baseline rate of targeted labs was 1.30 (SD 1.77) labs per physician per patient-day.[8]

Table 1 shows the associations between dashboard use and participant characteristics. Participants who deviated from the service average by 1 SD of labs per patient-day had higher odds of opening the link to the dashboard (odds ratio [OR]: 1.48; 95% confidence interval [CI], 1.01-2.17; $P = 0.047$). Associations with other characteristics (direction of deviation from the mean, PGY level, first occurrence of intervention, weeks since the start of intervention, and other team members opening the link) were not significant.

We did not observe a statistically significant difference in routine laboratory ordering by dashboard use, although residents who opened the link to the dashboard ordered 0.26 fewer labs per doctor-patient-day than those who did not (95% CI, −0.77-0.25; $P = 0.31$). The greatest difference was observed on day 2 after the intervention, when lab orders were lower among dashboard users by 0.59 labs per doc-patient-day (95% CI, −1.41-0.24; $P = 0.16$) when compared with the residents who did not open the dashboard.

Table 2 displays the main themes generated from the resident focus groups and provides representative quotes. Focus groups were open to all residents, including those who were not randomized to receive the study intervention. A total of 23 residents participated in the focus groups. First, residents commented on the advantages of the dashboard intervention about test utilization. Specifically, they felt positively that it raised awareness about overuse, appreciated receiving

TABLE 2. Main Themes from Resident Focus Groups

Domain	Theme	Representative Quote
Usefulness of the laboratory dashboard	Raises awareness about laboratory ordering rates	"I don't think there's any question that it's interesting. It's super interesting to look at it and decide if you can derive meaningful information from it. I think it's definitely interesting, and I'd love to see it out of curiosity.
	Provides individual feedback	"It is nice to get data tailored to us."
	Can be reviewed quickly	"It really only takes a couple of minutes to go through."
Barriers to using this dashboard intervention	Does not account for patient complexity	"I would be a little bit annoyed actually, because it takes into account none of the complexity of your patients."
	Sample size/duration on service	"There are almost no circumstances where I would care about a 1-week interval or a 2-week interval. It would be essentially impossible for me to be convinced that it was statistically relevant and that somehow you could account for all of the variants. But I would be interested in a longer time interval."
	Too simplistic	"It really takes all of the thinking out of it and just is glossing over the numbers, which I think could be a little bit frustrating."
	Reliability of data	"You have to order troponin three times because they're like oh, I didn't order that one. But if you put it in again, and you get three troponin orders, and the last one is the one that gets drawn."
	Delivery of intervention	"I currently have 5900 unread messages in my email box, so I'm going to say no."
	Superfluous to traditional training	"We've gone through several years of medical training and hopefully are able to sort of triage which labs you think are necessary for our patients or not."
	Laboratory orders are not under resident control	"I feel like there's just too many variables, and on top of that, what can you really control in it that's going to give you these metrics that either give you a false sense of doing well or make you feel like you're doing poorly when in reality it probably has very little to do with you. I'd rather get feedback from nursing staff and from phlebotomy and from the social workers that leave direct comments about how you interact with them in your performance as colleagues and your social skills and communication skills."
Barriers to using dashboards in general	Lack of time in resident schedule	"It's honestly just a time issue. If you can see everything in one screen, that's a lot easier than while you're on your phone trying to log into a different screen or remembering a password"
	Insufficient patient volume	"My preceptor is always like don't pay attention to this because you don't see enough patients for it to be useful at this point."
Suggestions to facilitate use of dashboards	Alleviate concerns about punitive consequences	"As long as people have the reassurance that this is really for your own benefit and to help you guide your practices and get some feedback, and not to punish you if you're low or even reward you if you're on the high end, but really just to kind of help you, I think people would maybe be more onboard."
	Additional guidance for how to use the data	"I don't know how it would change my practices...unless there was some guidance for us to do that."
	Ease of access	"I can read all this in an email - I'm much more likely to do that than log into a computer."
	Drop outlier patients or apply risk-adjustment	"I don't know if for each patient you could kind of score them based on how many active medical problems they have or the intensity of their problems and then kind of have a scale where you can compare patients between different – in a more objective fashion."
	Include other team members	"I think the difference is a lot in what the expectation is of the attending. So I think that maybe the target should be for this to go to the attendings on this teams, because they're the ones who are going to make that immediate culture change."

individualized feedback about their own practice, and liked that the data could be reviewed quickly. However, residents also expressed concerns about the design and implementation of the dashboard, including a lack of adjustment for patient complexity, small sample size, and time constraints limiting detailed dashboard exploration. Second, participants questioned the practicality of using such data-driven individualized feedback for training purposes in general, considering the low patient volume assigned to trainees and the sense that such feedback is too simplistic. For example, 1 participant commented, "…it really takes all of the thinking out of it and just is glossing over the numbers, which I think could be a little bit frustrating."

Third, participants identified barriers to using dashboards during training, including time constraints, insufficient patient volume, possible unanticipated consequences, and concerns regarding punitive action by the hospital administration or teaching supervisors. Suggestions to improve the uptake of practice feedback via dashboards included additional guidance for interpreting the data, exclusion of outlier cases or risk-adjustment, and ensuring ease of access to the data.

Last, participants also expressed enthusiasm toward receiving other types of individualized feedback data, including patient satisfaction, timing of discharges, readmission rates, utilization of consulting services, length of stay, antibiotic stewardship practices, costs and utilization data, and mortality or intensive care unit transfer rates (data not shown).

DISCUSSION

Overall, the engagement rates of internal medicine trainees with the online dashboard were low. Most residents did

open the e-mails containing the link and basic information about their utilization rates, but less than a quarter of them accessed the dashboard containing real-time data. Additionally, on average, it took them more than a day to do so. However, there is some indication that residents who deviated further from the mean in either direction, which was described in the body of the e-mail, were more motivated to investigate further and click the link to access the dashboard. This suggests that providing practice feedback in this manner may be effective for a subset of residents who deviate from the "typical practice," and as such, dashboards may represent a potential educational tool that could be aligned with practice-based learning competencies.

The focus groups provided important context about residents' attitudes toward EMR-based dashboards. Overall, residents were enthusiastic about receiving information regarding their personal laboratory ordering, both in terms of preventing iatrogenic harm and waste of resources. This supports previous research that found that both medical students and residents overwhelmingly believe that the overuse of labs is a problem and that there may be insufficient focus on cost-conscious care during training.[9,10] However, many residents questioned several aspects of the specific intervention used in this study and suggested that significant improvements would need to be made to future dashboards to increase their utility.

To our knowledge, this is the first attempt to evaluate resident engagement and attitudes toward receiving practice-based feedback via an EMR-based online dashboard. Previous efforts to influence resident laboratory ordering behavior have primarily focused on didactic sessions, financial incentives, price transparency, and repeated e-mail messaging containing summary statistics about ordering practices and peer comparisons.[11-14] While some prior studies observed success in decreasing unnecessary use of laboratory tests, such efforts are challenging to implement routinely on a teaching service with multiple rotating providers and may be difficult to replicate. Future iterations of dashboards that incorporate focused curriculum design and active participation of teaching attendings require further study.

This study has several limitations. The sample size of physicians is relatively small and consists of residents at a single institution. This may limit the generalizability of the results. Additionally, the dashboard captured laboratory-ordering rates during a 2-week block on an inpatient medicine service and was not adjusted for factors such as patient case mix. However, the rates were adjusted for patient volume. In future iterations of utilization dashboards, residents' concerns about small sample size and variability in clinical severity could be addressed through the adoption of risk-adjustment methodologies to balance out patient burden. This could be accomplished using currently available EMR data, such as diagnosis related groups or diagnoses codes to adjust for clinical complexity or report expected length of stay as a surrogate indicator of complexity.

Because residents are expected to be responsive to feedback, their use of the dashboards may represent an upper bound on physician responsiveness to social comparison feedback regarding utilization. However, e-mails alone may not be an effective way to provide feedback in areas that require additional engagement by the learner, especially given the volume of e-mails and alerts physicians receive. Future efforts to improve care efficiency may try to better capture baseline ordering rates, follow resident ordering over a longer period of time, encourage hospital staff to review utilization information with trainees, integrate dashboard information into regular performance reviews by the attendings, and provide more concrete feedback from attendings or senior residents for how this information can be used to adjust behavior.

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Two-Unit Red Cell Transfusions in Stable Anemic Patients

Rajiv N. Thakkar, MD[1], Stanley J. Podlasek, MD[2], Leo C. Rotello, MD[1], Paul M. Ness, MD[2], Steven M. Frank, MD[3*]

[1]Department of Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland; [2]Department of Pathology, Division of Transfusion Medicine, The Johns Hopkins Medical Institutions, Baltimore, Maryland; [3]Department of Anesthesiology and Critical Care Medicine and the Armstrong Institute for Patient Safety and Quality, The Johns Hopkins Medical Institutions, Baltimore, Maryland.

The "Things We Do for No Reason" (TWDFNR) series reviews practices which have become common parts of hospital care but which may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent "black and white" conclusions or clinical practice standards, but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

INTRODUCTION

Blood transfusion is not only the most common procedure performed in US hospitals but is also widely overused, according to The Joint Commission. Unnecessary transfusions can increase risks and costs, and now, multiple landmark trials support using restrictive transfusion strategies. This manuscript discusses the importance and potential impacts of giving single-unit red blood cell (RBC) transfusions in anemic patients who are not actively bleeding and are hemodynamically stable. The "thing we do for no reason" is giving 2-unit RBC transfusions when 1 unit would suffice. We call this the "Why give 2 when 1 will do?" campaign for RBC transfusion.

CASE PRESENTATION

A 74-year-old, 70-kg male with a known history of myelodysplastic syndrome is admitted for dizziness and shortness of breath. His hemoglobin (Hb) concentration is 6.2 g/dL (baseline Hb of 8 g/dL). The patient denies any hematuria, hematemesis, and melena. Physical examination is remarkable only for tachycardia—heart rate of 110. The admitting hospitalist ponders whether to order a 2-unit red blood cell (RBC) transfusion.

WHY YOU MIGHT THINK DOUBLE UNIT RED BLOOD CELL TRANSFUSIONS ARE HELPFUL

RBC transfusion is the most common procedure performed in US hospitals, with about 12 million RBC units given to patients in the United States each year.[1] Based on an opinion paper published in 1942 by Adams and Lundy[2] the "10/30 rule" set the standard that the ideal transfusion thresholds were an Hb of 10 g/dL or a hematocrit of 30%. Until human immunodeficiency virus (HIV) became a threat to the nation's blood supply in the early 1980s, few questioned the 10/30 rule. There is no doubt that blood transfusions can be lifesaving in the presence of active bleeding or hemorrhagic shock; in fact, many hospitals have blood donation campaigns reminding us to "give blood—save a life." To some, these messages may suggest that more blood is better. Prior to the 1990s, clinicians were taught that if the patient needed an RBC transfusion, 2 units was the optimal dose for adult patients. In fact, single-unit transfusions were strongly discouraged, and authorities on the risks of transfusion wrote that single-unit transfusions were acknowledged to be unnecessary.[3]

WHY THERE IS "NO REASON" TO ROUTINELY ORDER DOUBLE UNIT TRANSFUSIONS

According to a recent Joint Commission Overuse Summit, transfusion was identified as 1 of the top 5 overused medical procedures.[4] Blood transfusions can cause complications such as transfusion-related acute lung injury and transfusion-associated circulatory overload, the number 1 and 2 causes of transfusion-related deaths, respectively,[5] as well as other transfusion reactions (eg, allergic and hemolytic) and alloimmunization. Transfusion-related morbidity and mortality have been shown to be dose dependent,[6] suggesting that the lowest effective number of units should be transfused. Although, with modern-day testing, the risks of HIV and viral hepatitis are exceedingly low, emerging infectious diseases such as the Zika virus and Babesiosis represent new threats to the nation's blood supply, with potential transfusion-related transmission and severe consequences, especially for the immunosuppressed. As quality-improvement, patient safety, and cost-saving initiatives, many hospitals have implemented strategies to reduce unnecessary transfusions and decrease overall blood utilization.

In the past decade, clinicians have begun to realize that blood is like any other therapeutic agent; it is not without risk, it has a cost, and it should be given only when indicated and at the lowest effective dose. Guidelines and recommendations have shifted toward single-unit RBC transfusions in hemodynamically stable, nonbleeding patients.[7,8] The American Association of Blood Banks (AABB) supports single-unit transfusions for such patients.[9] Unfortunately, many clinicians are unaware of this recommendation.[10]

***Address for correspondence and reprint requests:** Steven M. Frank, MD, Zayed 6208, Johns Hopkins Hospital, 1800 Orleans St., Baltimore, MD 21287; Telephone: 410-955-8465, Fax: 410-955-0994; E-mail: sfrank3@jhmi.edu

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TABLE. Eight Prospective Randomized Trials Comparing Restrictive and Liberal Red Blood Cell Transfusion Strategies

Clinical Trial	Patient Population	Restrictive Strategy (Hb Trigger, Target)	Liberal Strategy (Hb Trigger, Target)	Reduction in Blood Utilization	Clinical Outcomes			
					Event	Restrictive (Incidence)	Liberal (Incidence)	*P* Value
Hebert et al., 1999[11] (n = 838)	Critically ill (adults)	7 to 8.5 g/dL	10 to 10.7 g/dL	54% fewer RBC units transfused	• 30-day mortality (all)	18.7%	23.3%	.11
					• 30-day mortality (age <55 years)	5.7%	13.0%	.02
					• 30-day mortality (APACHE II score ≤20)	8.7%	16.1%	.03
					• In-hospital mortality	22.2%	28.1%	.05
Lacroix et al., 2007[13] (n = 637)	Critically ill (pediatric)	7 to 9.4 g/dL	9.5 to 11.2 g/dL	47% fewer RBC units transfused	In-hospital Multiple-organ dysfunction syndrome	12%	12%	NS
Hajjar et al., 2010[12] (n = 502)	Cardiac surgery (adults)	8.0 to 9.1 g/dL	10 to 10.5 g/dL	58% fewer RBC units transfused	30-day composite all-cause mortality and severe morbidity	11%	10%	.85
Carson et al., 2011[14] (n = 2016)	Femur fracture (elderly adults)	8.0 to 9.5 g/dL	10.0 to 11.0 g/dL	65% fewer RBC units transfused	Composite endpoint	34.7%	35.2%	NS
					• 60-day mortality	28.1%	27.6%	NS
					• 60-day inability to walk	6.6%	7.6%	NS
Villanueva et al., 2013[15] (n = 921)	Gastrointestinal bleeding (adults)	7 to 9.2 g/dL	9 to 10.1 g/dL	59% fewer RBC units transfused	45-day all-cause mortality	5%	9%	.02
Robertson et al., 2014[17] (n = 200)	Traumatic brain injury	7 to 9.7 g/dL	10 to 11.4 g/dL	49% fewer RBC units transfused	• Favorable Glasgow Outcome Scale	42.5%	33.0%	.28
					• Thrombotic events	8.1%	21.8%	.009
Holst LB et al. 2014[16] (n = 998)	Septic shock (adults)	7 to 7.5 g/dL	9 to 9.5 g/dL	50% fewer RBC units transfused	90-day all-cause mortality	43.0%	45.0%	.44
Murphy GL et al., 2015[18] (n = 2007)	Cardiac surgery (adults)	7.5 to 9 g/dL	9.0 to 10 g/dL	40% fewer RBC units transfused	90-day serious infections or ischemic event	35.1%	33.0%	.30

NOTE: All studies employed single-unit RBC transfusion strategies except Robertson et al.[17] (unspecified strategy) and Lacroix et al.[13] (weight-based pediatric transfusions). Overall, no study showed an improved primary outcome using a liberal transfusion strategy. Villanueva et al.[15] showed a worse primary outcome (increased mortality) using a liberal transfusion strategy. Hebert et al.[11] showed a worse primary outcome in the 2 subgroups shown using a liberal strategy. Robertson et al.[17] showed a worse secondary outcome (thrombotic events) using a liberal strategy. Abbreviations: Hb, hemoglobin; NS, not significant; RBC, red blood cell.

This change in practice is evidence based and supported by 8 large, randomized trials that compared a restrictive to a liberal transfusion strategy, which are summarized in the Table.[11-18] These trials support (1) an Hb transfusion trigger of 7-8 g/dL and (2) transfusion of 1 RBC unit at a time, followed by reassessment of the Hb level and patient status. Five of the trials found no difference in the primary outcome[12-14,16,18] (meaning no benefit to giving more blood than is needed), and 3 of the trials showed worse outcomes with liberal transfusion[11,15,17] (or actual harm from giving extra blood). One issue to consider is that these clinical trials were focused on the Hb trigger (ie, defined as the Hb level at which clinicians start giving blood) but not on the Hb target (ie, the Hb level at which clinicians stop giving blood). The difference between the trigger and the target is determined by the dose of blood. In these trials, the standard strategy for transfusion was a single RBC unit followed by reassessment.

The above-mentioned studies support the concept that oftentimes less is more for transfusions, which includes giving the lowest effective amount of transfused blood. These trials have enrolled multiple patient populations, such as critically ill patients in the intensive care unit,[11,13] elderly orthopedic surgery patients,[14] cardiac surgery patients,[12] and patients with gastrointestinal hemorrhage,[15] traumatic brain injury,[17] and septicemia.[16] Outcomes in the trials included mortality, serious infections, thrombotic and ischemic events, neurologic deficits, multiple-organ dysfunction, and inability to ambulate (Table). The findings in these studies suggest that we increase risks and cost without improving outcomes only by giving more blood than is necessary. Since most of these trials were published in the last decade, some very recently, clinicians have not fully adopted these newer, restrictive transfusion strategies.[19]

ARE THERE REASONS TO ORDER 2-UNIT TRANSFUSIONS IN CERTAIN CIRCUMSTANCES?

Perhaps the most common indication for ordering multiunit RBC transfusions is active bleeding, as it is clear that whatever Hb threshold is chosen, transfusion should be given in sufficient amounts to stay ahead of the bleeding.[20] It is important to remember that we treat patients and their symptoms, not just their laboratory values. Good medical care adapts and/or modifies treatment protocols and guidelines according to the clinical situation. Intravascular volume is

also important to consider because what really matters for oxygen content and delivery is the total red cell mass (ie, the Hb concentration times the blood volume). If a patient is hypovolemic and/or actively bleeding, the Hb transfusion trigger, as well as the dose of blood, may need to be adjusted upward, creating clinical scenarios in which 2-unit RBC transfusions may be appropriate. Other clinical settings for which multiunit RBC transfusions may be indicated include patients with severe anemia, for whom both the pretransfusion Hb (the trigger) and the posttransfusion Hb (the target) should be considered. Patients with hemoglobinopathies (eg, sickle cell or thalassemia) sometimes require multiunit transfusions or even exchange transfusions to improve oxygen delivery. Other patients who may benefit from higher Hb levels achieved by multiunit transfusions include those with acute coronary syndromes; however, the ideal Hb transfusion threshold in this setting has yet to be determined.[21]

WHAT YOU SHOULD DO INSTEAD

For hemodynamically stable patients and in the absence of active bleeding, single-unit RBC transfusions, followed by reassessment, should be the standard for most patients. The reassessment should include measuring the posttransfusion Hb level and checking for improvement in vital sign abnormalities and signs or symptoms of anemia or end-organ ischemia. A recent publication on our hospital-wide campaign called "Why give 2 when 1 will do?" showed a significant (35%) reduction in 2-unit transfusion orders along with an 18% overall decrease in RBC utilization and substantial cost savings (≈$600,000 per year).[10] These findings demonstrate that there is a large opportunity to reduce transfusion overuse by encouraging single-unit transfusions.

RECOMMENDATIONS

- For nonbleeding, hemodynamically stable patients who require a transfusion, transfuse a single RBC unit and then reassess the Hb level before transfusing a second unit.
- The decision to transfuse RBCs should take into account the patient's overall condition, including their symptoms, intravascular volume, and the occurrence and rate of active bleeding, not just the Hb value alone.

CONCLUSIONS

In stable patients, a single unit of RBCs often is adequate to raise the Hb to an acceptable level and relieve the signs and symptoms of anemia. Additional units should be prescribed only after reassessment of the patient and the Hb level. For our patient with symptomatic anemia, it is reasonable to transfuse 1 RBC unit, and then measure the Hb level, and reassess his symptoms before giving additional RBC units.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason?" Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and liking it on Facebook. We invite you to propose ideas for other "Things We Do for No Reason" topics by emailing TWDFNR@hospitalmedicine.org.

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Mass Confusion

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

Cybele L. Abad, MD[1], Gurpreet Dhaliwal, MD[2,3], Michael D. Geschwind, MD, PhD[4], Sanjay Saint, MD, MPH[5], Nasia Safdar, MD, PhD[6*]

[1]Department of Medicine, University of the Philippines-Philippine General Hospital, Manila, Philippines; [2]Department of Medicine, University of California San Francisco, San Francisco, California; [3]Medical Service, San Francisco VA Medical Center, San Francisco, California; [4]Memory and Aging Center, Department of Neurology, University of California San Francisco, San Francisco, California; [5]Department of Veterans Affairs Medicine Service and Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan; [6]William S. Middleton Memorial Veterans Hospital and Department of Medicine, University of Wisconsin-Madison School of Medicine, Madison, Wisconsin.

A 57-year-old woman presented to the emergency department of a community hospital with a 2-week history of dizziness, blurred vision, and poor coordination following a flu-like illness. Symptoms were initially attributed to complications from a presumed viral illness, but when they persisted for 2 weeks, she underwent magnetic resonance imaging (MRI) of the brain, which was reported as showing a 2.4 x 2.3 x 1.9 cm right frontal lobe mass with mild mass effect and contrast enhancement (Figure 1). She was discharged home at her request with plans for outpatient follow-up.

A flu-like illness followed by diffuse neurologic symptoms suggests that a pathogen, most likely viral, may have either directly invaded the central nervous system (CNS) or incited an immune reaction causing an encephalitis. Bacterial pharyngitis, sinusitis, otitis, or pneumonia could similarly have spread to the brain hematogenously or contiguously, leading to a brain abscess. Some immune encephalitides, such as anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis, have a flu-like prodrome, although none would have a mass lesion with contrast enhancement. A postviral infectious or inflammatory cerebellitis could cause dizziness, visual disturbance, and incoordination.

Brain masses are usually neoplastic, infectious, or less commonly, inflammatory. The isolated lesion in the right frontal lobe is unlikely to explain her symptoms, which are more suggestive of multifocal disease or elevated intracranial pressure. Although the frontal eye fields could be affected by the mass, such lesions usually cause tonic eye deviation, not blurry vision; furthermore, coordination, which is impaired here, is not governed by the frontal lobe.

Two weeks later, she returned to the same emergency department with worsening symptoms and new bilateral upper extremity dystonia, confusion, and visual hallucinations. Cerebrospinal fluid (CSF) analysis revealed clear, nonxanthochromic fluid with 4 nucleated cells (a differential was not performed), 113 red blood cells, glucose of 80 mg/dL (normal range, 50-80 mg/dL), and protein of 52 mg/dL (normal range, 15-45 mg/dL).

Confusion is generally caused by a metabolic, infectious, structural, or toxic etiology. Standard CSF test results are usually normal with most toxic or metabolic encephalopathies. The absence of significant CSF inflammation argues against infectious encephalitis; paraneoplastic and autoimmune encephalitis, however, are still possible. The CSF red blood cells were likely due to a mildly traumatic tap, but also may have arisen from the frontal lobe mass or a more diffuse invasive process, although the lack of xanthochromia argues against this. Delirium and red blood cells in the CSF should trigger consideration of herpes simplex virus (HSV) encephalitis, although the time course is a bit too protracted and the reported MRI findings do not suggest typical medial temporal lobe involvement.

The disparate neurologic findings suggest a multifocal process, perhaps embolic (eg, endocarditis), ischemic (eg, intravascular lymphoma), infiltrative (eg, malignancy, neurosarcoidosis), or demyelinating (eg, postinfectious acute disseminated encephalomyelitis, multiple sclerosis). However, most of these would have been detected on the initial MRI. Upper extremity dystonia would likely localize to the basal ganglia, whereas confusion and visual hallucinations are more global. The combination of a movement disorder and visual hallucinations is seen in Lewy body dementia, but this tempo is not typical.

Although the CSF does not have pleocytosis, her original

***Address for correspondence and reprint requests:** Nasia Safdar, MD, PhD, University of Wisconsin School of Medicine and Public Health, 600 Highland Avenue, Madison, WI 53792; Telephone: 608-263-1545; Fax: 608-263-4464; E-mail: ns2@medicine.wisc.edu

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symptoms were flu-like; therefore, CSF testing for viruses (eg, enterovirus) is reasonable. Bacterial, mycobacteria, and fungal studies are apt to be unrevealing, but CSF cytology, IgG index, and oligoclonal bands may be useful. Should the encephalopathy progress further and the general medical evaluation prove to be normal, then tests for autoimmune disorders (eg, antinuclear antibodies, NMDAR, paraneoplastic disorders) and rare causes of rapidly progressive dementias (eg, prion diseases) should be sent.

Additional CSF studies including HSV polymerase chain reaction (PCR), West Nile PCR, Lyme antibody, paraneoplastic antibodies, and cytology were sent. Intravenous acyclovir was administered. The above studies, as well as Gram stain, acid-fast bacillus stain, fungal stain, and cultures, were negative. She was started on levetiracetam for seizure prevention due to the mass lesion. An electroencephalogram (EEG) was reported as showing diffuse background slowing with superimposed semiperiodic sharp waves with a right hemispheric emphasis. Intravenous immunoglobulin (IVIG) 0.4 mg/kg/day over 5 days was administered with no improvement. The patient was transferred to an academic medical center for further evaluation.

The EEG reflects encephalopathy without pointing to a specific diagnosis. Prophylactic antiepileptic medications are not indicated for CNS mass lesions without clinical or electrophysiologic seizure activity. IVIG is often administered when an autoimmune encephalitis is suspected, but the lack of response does not rule out an autoimmune condition.

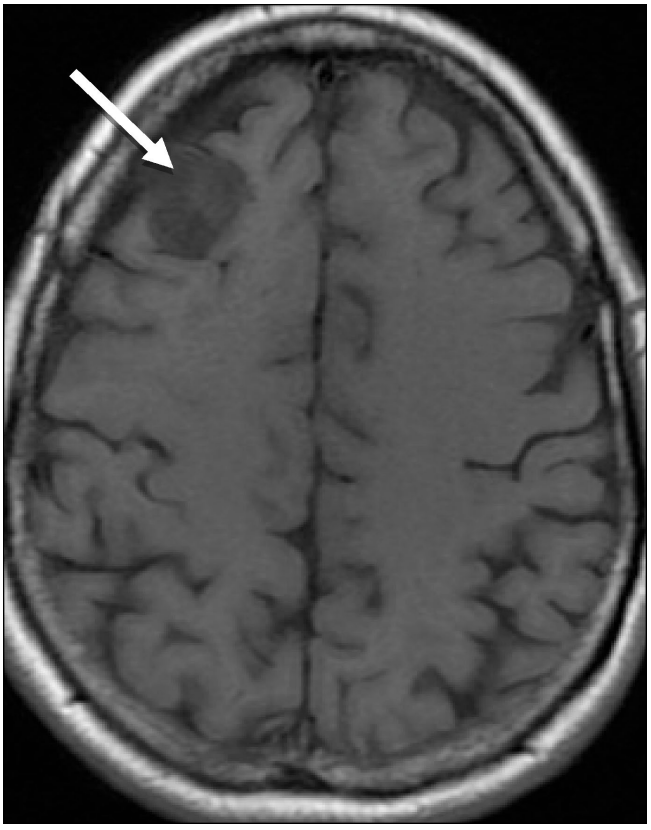

FIG 1. There is a 2.4 x 2.3 x 1.9 cm mass in the right frontal lobe (arrow).

Her medical history included bilateral cataract extraction, right leg fracture, tonsillectomy, and total abdominal hysterectomy. She had a 25-year smoking history and a family history of lung cancer. She had no history of drug or alcohol use. On examination, her temperature was 37.9°C, blood pressure of 144/98 mm Hg, respiratory rate of 18 breaths per minute, a heart rate of 121 beats per minute, and oxygen saturation of 97% on ambient air. Her eyes were open but she was nonverbal. Her chest was clear to auscultation. Heart sounds were distinct and rhythm was regular. Abdomen was soft and nontender with no organomegaly. Skin examination revealed no rash. Her pupils were equal, round, and reactive to light. She did not follow verbal or gestural commands and intermittently tracked with her eyes, but not consistently enough to characterize extraocular movements. Her face was symmetric. She had a normal gag and blink reflex and an increased jaw jerk reflex. Her arms were flexed with increased tone. She had a positive palmo-mental reflex. She had spontaneous movement of all extremities. She had symmetric, 3+ reflexes of the patella and Achilles tendon with a bilateral Babinski's sign. Sensation was intact only to withdrawal from noxious stimuli.

The physical exam does not localize to a specific brain region, but suggests a diffuse brain process. There are multiple signs of upper motor neuron involvement, including increased tone, hyperreflexia, and Babinski (plantar flexion) reflexes. A palmo-mental reflex signifies pathology in the cerebrum. Although cranial nerve testing is limited, there are no features of cranial neuropathy; similarly, no pyramidal weakness or sensory deficit has been demonstrated on limited testing. The differential diagnosis of her rapidly progressive encephalopathy includes autoimmune or paraneoplastic encephalitis, diffuse infiltrative malignancy, metabolic diseases (eg, porphyria, heavy metal intoxication), and prion disease.

Her family history of lung cancer and her smoking increases the possibility of paraneoplastic encephalitis, which often has subacute behavioral changes that precede complete neurologic impairment. Inflammatory or hemorrhagic CSF is seen with *Balamuthia* amoebic infection, which causes a granulomatous encephalitis and is characteristically associated with a mass lesion. Toxoplasmosis causes encephalitis that can be profound, but patients are usually immunocompromised and there are typically multiple lesions.

Laboratory results showed a normal white blood cell count and differential, basic metabolic profile and liver function tests, and C-reactive protein. Human immunodeficiency virus antibody testing was negative. Chest radiography and computed tomography of chest, abdomen, and pel-

vis were normal. A repeat MRI of the brain with contrast was reported as showing a 2.4 x 2.3 x 1.9 cm heterogeneously enhancing mass in the right frontal lobe with an enhancing dural tail and underlying hyperostosis consistent with a meningioma, and blooming within the mass consistent with prior hemorrhage. No mass effect was present.

The meningioma was resected 3 days after admission but her symptoms did not improve. Routine postoperative MRI was reported to show expected postsurgical changes but no infarct. Brain biopsy at the time of the operation was reported as meningioma and mild gliosis without encephalitis.

The reported MRI findings showing unchanged size and overall appearance of the mass, its connection to the dura and skull, and the pathology results all suggest that the mass is a meningioma. There is no evidence of disease outside of the CNS. Some cancers that provoke a paraneoplastic response can be quite small yet may incite an immune encephalitis; anti-NMDAR-mediated encephalitis can occur with malignancy (often ovarian), although it also arises in the absence of any tumor. Any inclination to definitively exclude conditions not seen on the brain biopsy must be tempered by the limited sensitivity of brain histology examination. Still, what was not seen warrants mention: vascular inflammation suggestive of CNS vasculitis, granulomas that might point to neurosarcoidosis, malignant cells of an infiltrating lymphoma or glioma, or inflammatory cells suggestive of encephalitis. Prion encephalopathy remains possible.

The patient remained unresponsive. A repeat EEG showed bilateral generalized periodic epileptiform discharges with accompanying twitching of the head, face, and left arm, which were suppressed with intravenous propofol and levetiracetam. Three weeks following meningioma resection, a new MRI was read as showing new abnormal signal in the right basal ganglia, abnormality of the cortex on the diffusion weighted images, and progressive generalized volume loss.

Among the aforementioned diagnoses, focal or diffuse periodic epileptiform discharges at 1-2 hertz are most characteristic of prion disease. Striatal and cortical transverse relaxation time (T2)-weighted and diffusion-weighted imaging (DWI) hyperintensities with corresponding restricted diffusion is characteristic of Creutzfeldt-Jakob disease (CJD), although metabolic disorders, seizures, and encephalitis can very rarely show similar MRI findings. The clinical course, the MRI and EEG findings, and nondiagnostic biopsy results, which were initially not assessed for prion disease, collectively point to prion disease. Detection of abnormal prion protein in the brain tissue by immunohistochemistry or molecular methods would confirm the diagnosis.

Review of the original right frontal cortex biopsy specimen at the National Prion Disease Pathology Surveillance Center, including immunostaining with 3F4, a monoclonal antibody to the prion protein, revealed granular deposits typical of prion disease. This finding established a diagnosis of prion disease, likely sporadic CJD. The patient was transitioned to palliative care and died shortly thereafter.

Brain autopsy showed regions with transcortical vacuolation (spongiform change), other cortical regions with varying degrees of vacuolation, abundant reactive astrocytes, paucity of neurons, and dark shrunken neurons. Vacuolation and gliosis were observed in the striatum and were most pronounced in the thalamus. There was no evidence of an inflammatory infiltrate or a neoplastic process. These findings with the positive 3F4 immunohistochemistry and positive Western blot from brain autopsy, as well as the absence of a mutation in the prion protein gene, were diagnostic for CJD.

An investigation was initiated to track the nondisposable surgical instruments used in the meningioma resection that may have been subsequently used in other patients. It was determined that 52 neurosurgical patients may have been exposed to prion-contaminated instruments. The instruments were subsequently processed specifically for prion decontamination. After 7 years, no cases of CJD have been diagnosed in the potentially exposed patients.

DISCUSSION

CJD is a rare neurodegenerative condition[1] classified as one of the transmissible spongiform encephalopathies, so called because of the characteristic spongiform pattern (vacuolation) seen on histology, as well as the presence of neuronal loss, reactive gliosis in the gray matter, and the accumulation of the abnormal isoform of the cellular prion protein.[2] It affects about one person in every one million people per year worldwide; in the United States there are about 300 cases per year. The most common form of human prion disease, sporadic CJD, is relentlessly progressive and invariably fatal, and in most cases, death occurs less than 5 months from onset.[3] There is no cure, although temporizing treatments for symptoms can be helpful.

Sporadic CJD, which accounts for approximately 85% of all cases of prion disease in humans, typically manifests with rapidly progressive dementia and myoclonus after a prolonged incubation period in persons between 55 and 75 years of age. Genetic forms account for approximately 15% and acquired forms less than 1% of human prion diseases.[1] Prion diseases have a broad spectrum of clinical manifestations, including dementia, ataxia, parkinsonism, myoclonus, insomnia, paresthesias, and abnormal or changed behavior.[4] Given the protean clinical manifestations of prion diseases and rarity, the diagnosis is challenging to make antemortem. One recent study showed that most patients receive about 4 misdiagnoses and are often two-thirds of the way through their disease course before the correct diagnosis of sporadic CJD is made.[5]

T2-weighted high-signal intensity abnormalities in a cortical distribution and/or deep nuclei, seen best with diffusion-weighted imaging MRI,[6] should raise the possibility of CJD in the correct clinical context. Retrospective analysis of

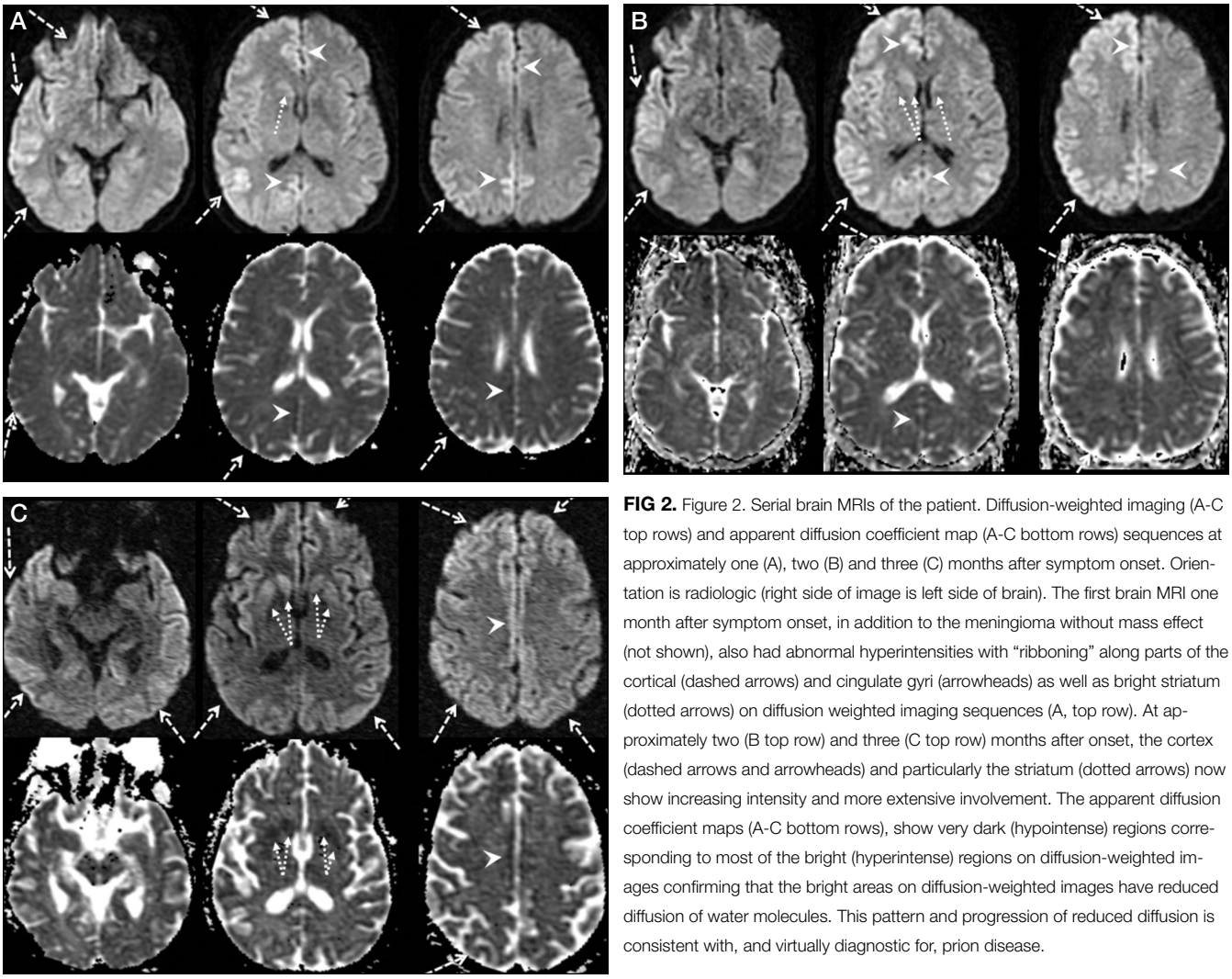

FIG 2. Figure 2. Serial brain MRIs of the patient. Diffusion-weighted imaging (A-C top rows) and apparent diffusion coefficient map (A-C bottom rows) sequences at approximately one (A), two (B) and three (C) months after symptom onset. Orientation is radiologic (right side of image is left side of brain). The first brain MRI one month after symptom onset, in addition to the meningioma without mass effect (not shown), also had abnormal hyperintensities with "ribboning" along parts of the cortical (dashed arrows) and cingulate gyri (arrowheads) as well as bright striatum (dotted arrows) on diffusion weighted imaging sequences (A, top row). At approximately two (B top row) and three (C top row) months after onset, the cortex (dashed arrows and arrowheads) and particularly the striatum (dotted arrows) now show increasing intensity and more extensive involvement. The apparent diffusion coefficient maps (A-C bottom rows), show very dark (hypointense) regions corresponding to most of the bright (hyperintense) regions on diffusion-weighted images confirming that the bright areas on diffusion-weighted images have reduced diffusion of water molecules. This pattern and progression of reduced diffusion is consistent with, and virtually diagnostic for, prion disease.

MRIs of patients who are ultimately diagnosed with CJD often shows pathognomonic MRI findings, but these changes can be subtle and are challenging for clinicians or radiologists who are unfamiliar with such a rare disorder to detect in real time.[7] Review of the sequential MRIs in this case (Figure 2) by a prion expert on our author team (M.G.) revealed on DWI and T2-weighted sequences focal asymmetric (right greater than left) cortical hyperintensities with more subtle asymmetric striatal hyperintensity, which progressed to other regions on subsequent studies. Histopathological examination of a brain specimen remains the definitive diagnostic procedure,[2] but brain biopsy carries its own risk, and the diagnosis may still be missed if the disease is not suspected, as seen with our patient during the initial pathological analysis.

Testing for protein markers of rapid neuronal injury[8] in the CSF including 14-3-3, total tau, and neuron-specific enolase can increase suspicion for CJD, although there is a 10%-50% false positive rate with these markers.[9] In this case, those tests were not performed; positive results would have been even more nonspecific in the setting of an enhancing brain mass and recent brain surgery.

Although not available at the time this patient was evaluated, the real-time quaking-induced conversion (RT-QuIC) test performed in CSF is diagnostically helpful, and, if positive, supportive of the MRI findings. The sensitivity and specificity of this test have been reported to be between 87%-91% and 98%-100%, respectively, albeit with limited data.[10] Applying RT-QuIC to nasal mucosal brushings might lead to even higher sensitivity and specificity.[11]

Seeking a premortem diagnosis for a rare disease with no known cure may seem superfluous, but it has important implications for establishing prognosis, limiting subsequent diagnostic and therapeutic measures, and safeguarding of other patients and operating room personnel. Iatrogenic CJD has occurred following invasive procedures involving neurosurgical instrumentation.[12] CJD has been transmitted from grafts of dura mater, transplanted corneas, implantation of inadequately sterilized electrodes in the brain, and in the early 1980s, injections of contaminated pituitary hormones (particularly growth hormone) derived from human pituitary glands taken from cadavers. Since CJD was first described in the 1920s, less than 1% of human prion cases have been acquired iatrogenically.[13]

In patients with rapidly progressive cognitive decline who warrant brain biopsy or surgery, the probability of prion diseases should be assessed based on clinical information and the results of MRI, EEG, and CSF testing. If prion disease is plausible, World Health Organization[14] precautions should be employed for neuroinvasive procedures to reduce transmission risk. Disposable equipment should be used when possible, and nondisposable neurosurgical instruments should be quarantined until a nonprion disease diagnosis is identified, or should be regarded as contaminated and reprocessed using the aforementioned protocol.

This case highlights the challenges of seeking the correct diagnosis and its consequences, especially from an infection control perspective. The initial imaging finding of a mass lesion (a meningioma—which is a common incidental finding in older adults[15]) was a red herring that initially obscured the correct diagnosis. The patient's progressive cognitive decline, EEG results, and evolving MRI findings, however, prompted further scrutiny of the brain biopsy specimen that eventually steered the clinicians away from mass confusion to diagnostic certainty.

TEACHING POINTS

- Rapidly progressive dementias (RPD) are characterized by cognitive decline over weeks to months. The RPD differential diagnosis includes fulminant forms of common neurodegenerative disorders (eg, Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia spectrum), autoimmune encephalidites, CNS cancers, and prion disease.
- Sporadic CJD is the most common human prion disease. It is a rare neurodegenerative condition with onset usually between the ages of 50 and 70 years, and most commonly manifests with rapidly progressive dementia, ataxia, and myoclonus.
- Because of its protean manifestations, the diagnosis of CJD is difficult to make antemortem, and diagnosis is often delayed. Specialist evaluation of brain MRI DWI sequences and new CSF diagnostic tests may allow for earlier diagnosis, which has management and infection control implications.

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Morbo Serpentino

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.

This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

Helene Møller Nielsen, MD[1]*, Shakil Shakar, MD[1], Ulla Weinreich MD[1], Mary Hansen MD[2], Rune Fisker, MD[3], Thomas E. Baudendistel, MD[4], Paul Aronowitz MD[5]

[1]Department of Pulmonary Medicine, Aalborg University Hospital, Aalborg, Denmark; [2]Department of Pathology, Aalborg University Hospital, Aalborg, Denmark; [3]Department of Nuclear Medicine, Aalborg University Hospital, Aalborg, Denmark; [4]Department of Medicine, Kaiser Permanente, Oakland, California; [5]Department of Medicine, University of California, Davis, California.

A 58-year-old Danish man presented to an urgent care center due to several months of gradually worsening fatigue, weight loss, abdominal pain, and changes in vision. His abdominal pain was diffuse, constant, and moderate in severity. There was no association with meals, and he reported no nausea, vomiting, or change in bowel movements. He also said his vision in both eyes was blurry, but denied diplopia and said the blurring did not improve when either eye was closed. He denied dysphagia, headache, focal weakness, or sensitivity to bright lights.

Fatigue and weight loss in a middle-aged man are nonspecific complaints that mainly help to alert the clinician that there may be a serious, systemic process lurking. Constant abdominal pain without nausea, vomiting, or change in bowel movements makes intestinal obstruction or a motility disorder less likely. Given that the pain is diffuse, it raises the possibility of an intraperitoneal process or a process within an organ that is irritating the peritoneum.

Worsening of vision can result from disorders anywhere along the visual pathway, including the cornea (keratitis or corneal edema from glaucoma), anterior chamber (uveitis or hyphema), lens (cataracts, dislocations, hyperglycemia), vitreous humor (uveitis), retina (infections, ischemia, detachment, diabetic retinopathy), macula (degenerative disease), optic nerve (optic neuritis), optic chiasm, and the visual projections through the hemispheres to the occipital lobes. To narrow the differential diagnosis, it would be important to inquire about prior eye problems, to measure visual acuity and intraocular pressure, to perform fundoscopic and slit-lamp exams to detect retinal and anterior chamber disorders, respectively, and to assess visual fields. An afferent pupillary defect would suggest optic nerve pathology.

Disorders that could unify the constitutional, abdominal, and visual symptoms include systemic inflammatory diseases, such as sarcoidosis (which has an increased incidence among Northern Europeans), tuberculosis, or cancer. While diabetes mellitus could explain his visual problems, weight loss, and fatigue, the absence of polyuria, polydipsia, or polyphagia argues against this possibility.

The patient had hypercholesterolemia and type 2 diabetes mellitus. Medications were metformin, atorvastatin, and glimepiride. He was a former smoker with 23 pack-years and had quit over 5 years prior. He had not traveled outside of Denmark in 2 years and had no pets at home. He reported being monogamous with his same-sex partner for the past 25 years. He had no significant family history, and he worked at a local hospital as a nurse. He denied any previous ocular history.

On examination, the pulse was 67 beats per minute, temperature was 36.7 degrees Celsius, respiratory rate was 16 breaths per minute, oxygen saturation was 99% while breathing ambient air, and blood pressure was 132/78. Oropharynx demonstrated no thrush or other lesions. The heart rhythm was regular and there were no murmurs. Lungs were clear to auscultation bilaterally. Abdominal exam was normal except for mild tenderness upon palpation in all quadrants, but no masses, organomegaly, rigidity, or rebound tenderness were present. Skin examination revealed several subcutaneous nodules measuring up to 0.5 cm in diameter overlying the right and left posterolateral chest walls. The nodules were rubbery, pink, nontender, and not warm nor fluctuant. Visual acuity was reduced in both eyes. Extraocular movements were intact, and the pupils reacted to light and accommodated appropriately. The sclerae were injected bilaterally. The remainder of the cranial nerves and neurologic exam were normal. Due to the vision loss, the patient was referred to an ophthalmologist who diagnosed bilateral anterior uveitis.

***Address for correspondence and reprint requests:** Helene Møller Nielson, MD, Department of Pulmonary Medicine, Aalborg University Hospital, Denmark; Telephone: 459-766-4748; Fax: 459-762-6407; E-mail: hemoni@rn.dk.

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Though monogamous with his male partner for many years, it is mandatory to consider complications of human immunodeficiency virus infection (HIV). The absence of oral lesions indicative of a low CD4 count, such as oral hairy leukoplakia or thrush, does not rule out HIV disease. Additional history about his work as a nurse might shed light on his risk of infection, such as airborne exposure to tuberculosis or acquisition of blood-borne pathogens through a needle stick injury. His unremarkable vital signs support the chronicity of his medical condition.

Uveitis can result from numerous causes. When confined to the eye, uncommon hereditary and acquired causes are less likely. In many patients, uveitis arises in the setting of systemic infection or inflammation. The numerous infectious causes of uveitis include syphilis, tuberculosis, toxoplasmosis, cat scratch disease, and viruses such as HIV, West Nile, and Ebola. Among the inflammatory diseases that can cause uveitis are sarcoidosis, inflammatory bowel disease, systemic lupus erythematosus, Behçet disease, and Sjogren syndrome.

Several of these conditions, including tuberculosis and syphilis, may also cause subcutaneous nodules. Both tuberculosis and syphilis can cause skin and gastrointestinal disease. Sarcoidosis could involve the skin, peritoneum, and uvea, and is a possibility in this patient. The dermatologic conditions associated with sarcoidosis are protean and include granulomatous inflammation and nongranulomatous processes such as erythema nodosum. Usually the nodules of erythema nodosum are tender, red or purple, and located on the lower extremities. The lack of tenderness points away from erythema nodosum in this patient. Metastatic cancer can disseminate to the subcutaneous tissue, and the patient's smoking history and age mandate we consider malignancy. However, skin metastases tend to be hard, not rubbery.

A cost-effective evaluation at this point would include syphilis serologies, HIV testing, testing for tuberculosis with either a purified protein derivative test or interferon gamma release assay, chest radiography, and biopsy of 1 of the lesions on his back.

Laboratory data showed 12,400 white blood cells per cubic milliliter (64% neutrophils, 24% lymphocytes, 9% monocytes, 2% eosinophils, 1% basophils), hemoglobin 7.9 g/dL, mean corpuscular volume 85 fL, platelets 476,000 per cubic milliliter, C-reactive protein 43 mg/dL (normal < 8 mg/L), gamma-glutamyl-transferase 554 IU/L (normal range 0-45), alkaline phosphatase 865 U/L (normal range 60-200), and erythrocyte sedimentation rate (ESR) 71 mm per hour. International normalized ratio was 1.0, albumin was 3.0 mg/dL, activated partial thromboplastin time was 32 seconds (normal 22 to 35 seconds), and bilirubin was 0.3 mg/dL. Antibodies to HIV, hepatitis C, and hepatitis B surface antigen were not detectable. Electrocardiography (ECG) was normal. Plain radiograph of the chest demonstrated multiple nodular lesions bilaterally measuring up to 1 cm with no cavitation. There was a left pleural effusion.

The history and exam findings indicate a serious inflammatory condition affecting his lungs, pleura, eyes, skin, liver, and possibly his peritoneum. In this context, the elevated C-reactive protein and ESR are not helpful in differentiating inflammatory from infectious causes. The constellation of uveitis, pulmonary and cutaneous nodules, and marked abnormalities of liver tests in a middle-aged man of Northern European origin points us toward sarcoidosis. Pleural effusions are not common with sarcoidosis but may occur. However, to avoid premature closure, it is important to consider other possibilities.

Metastatic cancer, including lymphoma, could cause pulmonary and cutaneous nodules and liver involvement, but the chronic time course and uveitis are not consistent with malignancy. Tuberculosis is still a consideration, though one would have expected him to report fevers, night sweats, and, perhaps, exposure to patients with pulmonary tuberculosis in his job as a nurse. Multiple solid pulmonary nodules are also uncommon with pulmonary tuberculosis. Fungal infections such as histoplasmosis can cause skin lesions and pulmonary nodules but do not fit well with uveitis.

At this point, "tissue is the issue." A skin nodule would be the easiest site to biopsy. If skin biopsy was not diagnostic, computed tomography (CT) of his chest and abdomen should be performed to identify the next most accessible site for biopsy.

Esophagogastroduodenoscopy (EGD) and colonoscopy showed normal findings, and random biopsies from the stomach and colon were normal. CT of the chest, abdomen, and pelvis performed with the administration of intravenous contrast showed multiple solid opacities in both lung fields up to 1 cm, with enlarged mediastinal and retroperitoneal lymph nodes measuring 1 to 3 cm in diameter, a left pleural effusion, wall thickening in the right colon, and several nonspecific hypodensities in the liver. A punch biopsy taken from the right chest wall lesion demonstrated chronic inflammation without granulomas. The patient underwent CT-guided biopsy of 1 of the right-sided lung nodules, which revealed noncaseating granulomatous inflammation, fibrosis, and necrosis. Neither biopsy contained malignant cells, and additional stains revealed no bacteria, fungi, or acid fast bacilli.

The retroperitoneal and mediastinal adenopathy are indicative of a widely disseminated inflammatory process. Lymphoma continues to be a concern, though uveitis as an initial presenting problem would very unusual. Although biopsy of the chest wall lesion failed to demonstrate granulomatous inflammation, the most parsimonious explanation is that the skin and lung nodules are both related to a single systemic process.

Granulomas form in an attempt to wall off offending agents, whether foreign antigens (talc, certain medications), infectious agents, or self-antigens. Review of histopathology and microbiologic studies are useful first steps. Stains for bacteria, fungi, or acid-fast organisms may diagnose an infec-

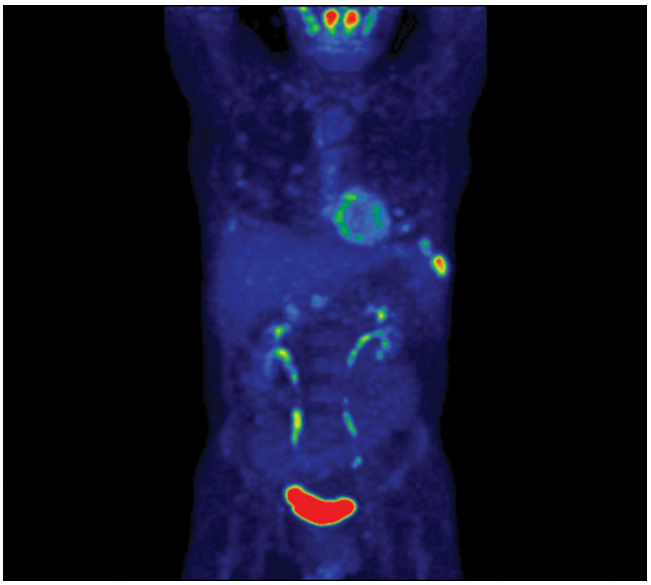

FIG 1. Three dimensional maximum intensity projection (MIP) 18F FDG PET demonstrating tracer activity in lymph nodes in the neck, and several foci in the lungs and costae. Physiological activity in the heart, kidneys, and bladder.

tious cause, such as tuberculosis, leprosy, syphilis, fungi, or cat scratch disease. Granulomas in association with vascular inflammation would indicate vasculitis. Other autoimmune considerations include sarcoidosis and Crohn disease. Non-caseating granulomas are typically found in sarcoidosis, cat scratch disease, syphilis, leprosy, or Crohn disease, but do not entirely exclude tuberculosis.

The negative infectious studies and lack of classic features of Crohn disease or other autoimmune diseases further point to sarcoidosis as the etiology of this patient's illness. A Norwegian dermatologist first described the pathology of sarcoidosis based upon specimens taken from skin nodules. He thought the lesions were sarcoma and described them as, "multiple benign sarcoid of the skin," which is where the name "sarcoidosis" originated.

Diagnosing sarcoidosis requires excluding other mimickers. Additional testing should include syphilis serologies, rheumatoid factor, and antineutrophilic cytoplasmic antibodies. The latter is associated with granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis, either of which may produce granulomatous inflammation of the lungs, skin, and uvea.

A positron emission tomography (PET)-CT demonstrated in Figure 1 shows bilateral increased fluorodeoxyglucose (FDG) uptake in the lungs, skin, and lymph nodes of the neck, mediastinum, and retroperitoneum, in addition to discrete FDG uptake in the liver. Furthermore, osteolytic changes were noted in several ribs.

At this juncture, PET-CT represents a costly and unnecessary test that does not narrow our diagnostic possibilities sufficiently to justify its use. Osteolytic lesions would be unusual in sarcoidosis and more likely in lymphoma or infectious processes such as tuberculosis. Tests for syphilis and tuberculosis are required, and are a fraction of the cost of a PET-CT.

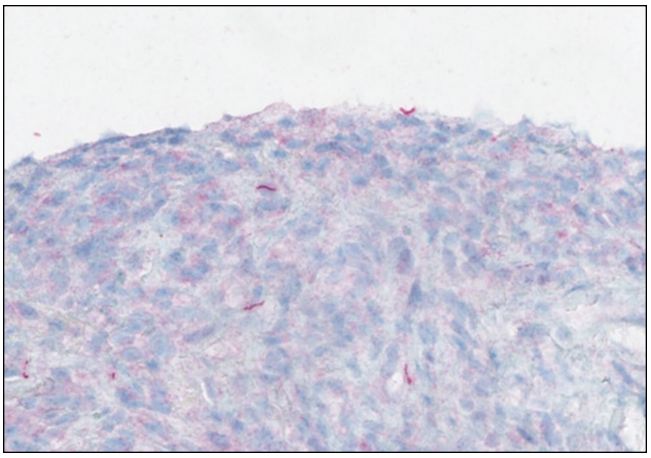

FIG 2. Lung core needle biopsy with spirochetes seen as elongated, delicate, coiling organisms. Immunohistochemical staining (red chromogen) for Treponema pallidum.

Another biopsy specimen was taken from a skin lesion on the left chest wall. Pathology revealed granulomatous inflammation again, and additional haematoxylin-eosin staining shown in Figure 2, which had not been performed on the previous specimens, demonstrated spirochetes. Serologies for syphilis were then obtained. Rapid plasma reagin (RPR) titer was elevated at 128, and IgM and IgG antibody tests to specific *Treponema pallidum* antigens were also elevated.

With the biopsy revealing spirochetes, and the positive results of a nontreponemal test (RPR) and confirmatory treponemal results, the diagnosis of syphilis is firmly established. Uveitis indicates neurosyphilis and warrants a longer course of intravenous penicillin. Lumbar puncture should be performed.

A lumbar puncture was performed. Cerebrospinal fluid (CSF) contained 9 white blood cells and 73 red blood cells per cubic milliliter; protein concentration was 73 mg/dL, and glucose was 116 mg/dL. Polymerase chain reaction for T. pallidum was negative. Transthoracic ECG and magnetic resonance imaging of the brain were normal. The patient was treated with intravenous penicillin G at 5 million units 4 times daily for 15 days. A PET-CT scan 3 months later revealed complete resolution of the subcutaneous, pulmonary, liver lesions, lymphadenopathy, and uveitis. Repeat treponemal serologies demonstrated a greater than 4-fold decline in titers.

DISCUSSION

Syphilis is a sexually transmitted disease with increasing incidence worldwide. Untreated infection progresses through

3 stages. The primary stage is characterized by the appearance of a painless chancre after an incubation period of 2 to 3 weeks. Four to 8 weeks later, the secondary stage emerges as a systemic infection, often heralded by a maculopapular rash with desquamation, frequently involving the soles and palms. Hepatitis, iridocyclitis, and early neurosyphilis may also be seen at this stage. Subsequently, syphilis becomes latent. One-third of patients with untreated latent syphilis will develop tertiary syphilis, typified by late neurosyphilis (tabes dorsalis and general paresis), cardiovascular disease (aortitis), or gummatous disease.[1]

Gummas are destructive granulomatous lesions that typically present indolently, may occur singly or multiply, and may involve almost any organ. It has been suggested that gummas are the immune system's defense to slow the bacteria after attempts to kill it have failed. Histologically, gummas are hyalinized nodules with surrounding granulomatous infiltrate of lymphocytes, plasma cells, and multinucleated giant cells with or without necrosis. In the preantibiotic era, gummas were seen in approximately 15% of infected patients, with a latency of 1 to 46 years after primary infection.[2] Penicillin led to a drastic reduction in gummas until the HIV epidemic, which led to the resurgence of gummas at a drastically shortened interval following primary syphilis.[3]

Most commonly, gummas affect the skin and bones. In the skin, lesions may be superficial or deep and may progress into ulcerative nodules. In the bones, destructive gummas have a characteristic "moth-eaten" appearance. Less common sequelae of gummas incude gummatous hepatitis, perforated nasal septum (saddle nose deformity), or hard palate erosions.[2,4] Rarely, syphilis involves the lungs, appearing as nodules, infiltrates, or pleural effusion.[5]

Ocular manifestations occur in approximately 5% of patients with syphilis, more often in secondary and tertiary stages, and are strongly associated with a spread to the central nervous system. Syphilis may affect any structure of the eye, with anterior uveitis as the most frequent manifestation. Partial or complete vision loss is identified in approximately half of the patients with ocular syphilis and may be completely reversed by appropriate treatment. Ophthalmologic findings such as optic neuritis and papilledema imply advanced illness, as do Argyll-Robertson pupils (small pupils that are poorly reactive to light, but with preserved accommodation and convergence).[6,7] The treatment of ocular syphilis is identical to that of neurosyphilis. The Centers for Disease Control and Prevention recommends CSF analysis in any patient with ocular syphilis. Abnormal results should prompt repeat lumbar puncture every 3 to 6 months following treatment until the CSF results normalize.[8]

The diagnosis of syphilis relies on indirect serologic tests. *T. pallidum* cannot be cultured in vitro, and techniques to identify spirochetes directly by using darkfield microscopy or DNA amplification via polymerase chain reaction are limited by availability or by poor sensitivity in advanced syphilis.[1] Imaging modalities including PET cannot reliably differentiate syphilis from other infectious and noninfectious mimickers.[9] Fortunately, syphilis infection can be diagnosed accurately based on reactive treponemal and nontreponemal serum tests. Nontreponemal tests, such as the RPR and Venereal Disease Research Laboratory, have traditionally been utilized as first-line evaluation, followed by a confirmatory treponemal test. However, nontreponemal tests may be nonreactive in a few settings: very early or very late in infection, and in individuals previously treated for syphilis. Thus, newer "reverse testing" algorithms utilize more sensitive and less expensive treponemal tests as the first test, followed by nontreponemal tests if the initial treponemal test is reactive.[8] Regardless of the testing sequence, in patients with no prior history of syphilis, reactive results on both treponemal and nontreponemal assays firmly establish a diagnosis of syphilis, obviating the need for more invasive and costly testing.

In patients with unexplained systemic illness, clinicians should have a low threshold to test for syphilis. Testing should be extended to certain asymptomatic individuals at higher risk of infection, including men who have sex with men, sexual partners of patients infected with syphilis, individuals with HIV or sexually-transmitted diseases, and others with high-risk sexual behavior or a history of sexually-transmitted diseases.[8] As the discussant points out, earlier consideration of and testing for syphilis would have spared the patient from unnecessary and costly EGD, colonoscopy, PET-CT scanning, and 3 biopsies.

Syphilis has been known to be a horribly destructive disease for centuries, earning the moniker "morbo serpentino" (serpentine disease) from the Spanish physician Ruiz Diaz de Isla in the 1500s.[10] In the modern era, physicians must remember to consider the diagnosis of syphilis in order to effectively mitigate the harm from this resurgent disease when it attacks our patients.

TEACHING POINTS

- Syphilis, the great imposter, is rising in incidence and should be on the differential diagnosis in all patients with unexplained multisystem inflammatory disease.
- A cost-effective diagnostic approach to syphilis entails serologic testing with treponemal and nontreponemal assays.
- Unexplained granulomas, especially in the skin, bone, or liver, should prompt consideration of gummatous syphilis.
- Ocular syphilis may involve any part of the visual tract and is treated the same as neurosyphilis.

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The Weekend Effect in Hospitalized Patients: A Meta-Analysis

Lynn A. Pauls, BS[1], Rebecca Johnson-Paben, BS[1], John McGready, PhD[2], Jamie D. Murphy, MD[1], Peter J. Pronovost, MD[1,3], PhD, Christopher L. Wu, MD[1,3]*

[1]*Department of Anesthesiology and Critical Care Medicine; The Johns Hopkins School of Medicine, Baltimore, Maryland;* [2]*The Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland;* [3]*Armstrong Institute for Patient Safety and Quality, Baltimore, Maryland.*

BACKGROUND: The presence of a "weekend effect" (increased mortality rate during Saturday and/or Sunday admissions) for hospitalized inpatients is uncertain.

PURPOSE: We performed a systematic review to examine the presence of a weekend effect on hospital inpatient mortality.

DATA SOURCES: PubMed, EMBASE, SCOPUS, and Cochrane databases (January 1966–April 2013) were utilized for our search.

STUDY SELECTION: We examined the mortality rate for hospital inpatients admitted during the weekend compared with those admitted during the workweek. To be included, the study had to provide discrete mortality data around the weekends (including holidays) versus weekdays, include patients who were admitted as inpatients over the weekend, and be published in English.

DATA EXTRACTION: The primary outcome was all-cause weekend versus weekday mortality with subgroup analysis by personnel staffing levels, rates and times to procedures rates and delays, or illness severity.

DATA SYNTHESIS: A total of 97 studies (N = 51,114,109 patients) were examined. Patients admitted on the weekends had a significantly higher overall mortality (relative risk, 1.19; 95% confidence interval, 1.14-1.23). With regard to the subgroup analyses, patients admitted on the weekends consistently had higher mortality than those admitted during the week, regardless of the levels of weekend/weekday differences in staffing, procedure rates and delays, and illness severity.

CONCLUSIONS: Hospital inpatients admitted during weekends may have a higher mortality rate compared with inpatients admitted during the weekdays. *Journal of Hospital Medicine* 2017;12:760-766. © 2017 Society of Hospital Medicine

The presence of a "weekend effect" (increased mortality rate during Saturday and/or Sunday admissions) for hospitalized inpatients is uncertain. Several observational studies[1-3] suggested a positive correlation between weekend admission and increased mortality, whereas other studies demonstrated no correlation[4-6] or mixed results.[7,8] The majority of studies have been published only within the last decade.

Several possible reasons are cited to explain the weekend effect. Decreased and presence of inexperienced staffing on weekends may contribute to a deficit in care.[7,9,10] Patients admitted during the weekend may be less likely to undergo procedures or have significant delays before receiving needed intervention.[11-13] Another possibility is that there may be differences in severity of illness or comorbidities in patients admitted during the weekend compared with those admitted during the remainder of the week. Due to inconsistency between studies regarding the existence of such an effect, we performed a meta-analysis in hospitalized inpatients to delineate whether or not there is a weekend effect on mortality.

***Address for correspondence and reprint requests:** Christopher Wu, MD, The Johns Hopkins Hospital, 1800 Orleans Street, Zayed 8-120, Baltimore, MD 21287; Telephone: 410-955-5608; E-mail: chwu@jhmi.edu.

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METHODS

Data Sources and Searches

This study was exempt from institutional review board review, and we utilized the recommendations from the Meta-analysis of Observational Studies in Epidemiology statement. We examined the mortality rate for hospital inpatients admitted during the weekend (weekend death) compared with the mortality rate for those admitted during the workweek (workweek death). We performed a literature search (January 1966–April 2013) of multiple databases, including PubMed, EMBASE, SCOPUS, and the Cochrane library (see Appendix). Two reviewers (LP, RJP) independently evaluated the full article of each abstract. Any disputes were resolved by a third reviewer (CW). Bibliographic references were hand searched for additional literature.

Study Selection

To be included in the systematic review, the study had to provide discrete mortality data on the weekends (including holidays) versus weekdays, include patients who were admitted as inpatients over the weekend, and be published in the English language. We excluded studies that combined weekend with weekday "off hours" (eg, weekday night shift) data, which could not be extracted or analyzed separately.

Data Extraction and Quality Assessment

Once an article was accepted to be included for the systematic review, the authors extracted relevant data if avail-

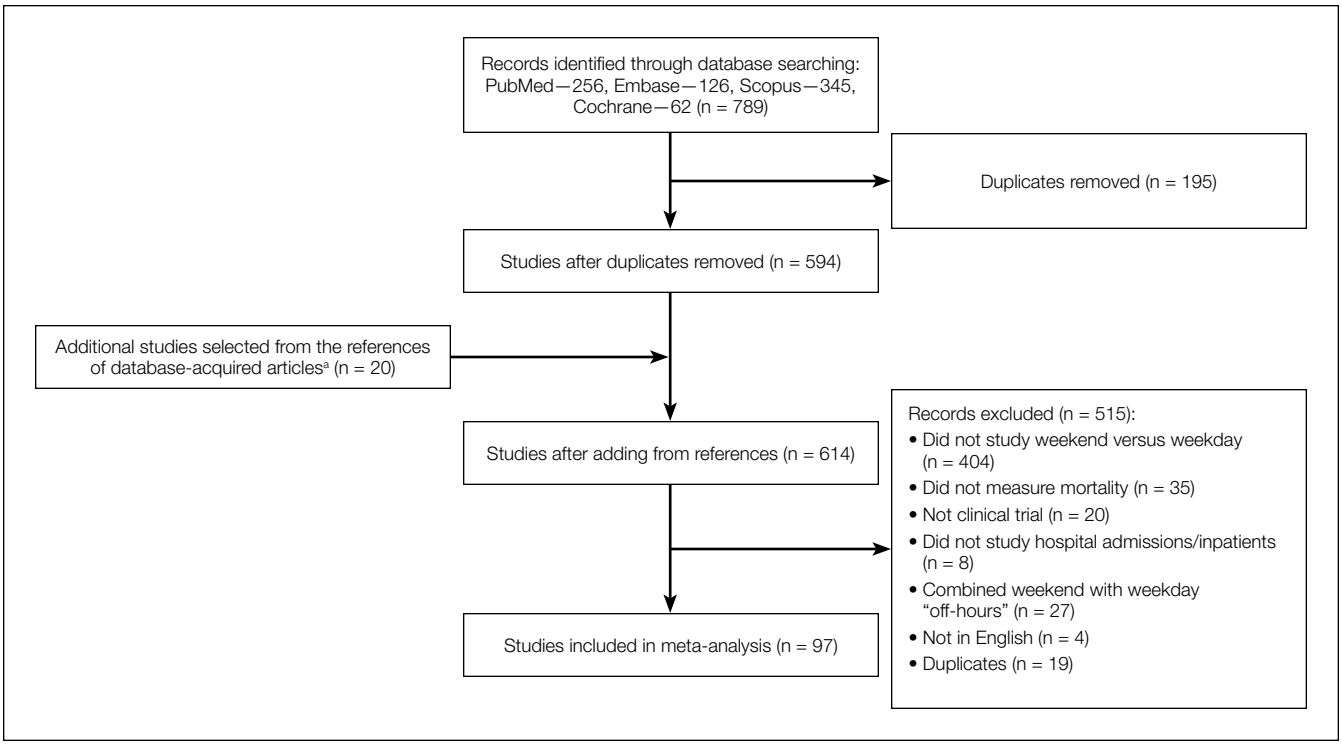

FIG 1. Flow diagram of studies selected for our meta-analysis.

[a]Records identified through database had their references checked for possible studies to include.

able, including study location, number and type of patients studied, patient comorbidity data, procedure-related data (type of procedure, difference in rate of procedure and time to procedure performed for both weekday and weekends), any stated and/or implied differences in staffing patterns between weekend and weekdays, and definition of mortality. We used the Newcastle-Ottawa Quality Assessment Scale to assess the quality of methodological reporting of the study.[14] The definition of weekend and extraction and classification of data (weekend versus weekday) was based on the original study definition. We made no attempt to impose a universal definition of "weekend" on all studies. Similarly, the definition of mortality (eg, 3-/7-/30-day) was based according to the original study definition. Death from a patient admitted on the weekend was defined as a "weekend death" (regardless of ultimate time of death) and similarly, death from a patient admitted on a weekday was defined as a "weekday death." Although some articles provided specific information on healthcare worker staffing patterns between weekends and weekdays, differences in weekend versus weekday staffing were implied in many articles. In these studies, staffing paradigms were considered to be different between weekend and weekdays if there were specific descriptions of the type of hospitals (urban versus rural, teaching versus nonteaching, large versus small) in the database, which would imply a typical routine staffing pattern as currently occurs in most hospitals (ie, generally less healthcare worker staff on weekends). We only included data that provided times (mean minutes/hours) from admission to the specific intervention and that provided actual rates of intervention performed for both weekend and weekday patients. We only included data that provided an actual rate of intervention performed for both weekend and weekday patients. With regard to patient comorbidities or illness severity index, we used the original studies classification (defined by the original manuscripts), which might include widely accepted global indices or a listing of specific comorbidities and/or physiologic parameters present on admission.

Data Synthesis and Analysis

We used a random effects meta-analysis approach for estimating an overall relative risk (RR) and risk differences of mortality for weekends versus weekdays, as well as subgroup specific estimates, and for computing confidence limits. The DerSimonian and Laird approach was used to estimate the random effects. Within each of the 4 subgroups (weekend staffing, procedure rates and delays, illness severity), we grouped each qualified individual study by the presence of a difference (ie, difference, no difference, or mixed) and then pooled the mortality rates for all of the studies in that group. For instance, in the subgroup of staffing, we sorted available studies by whether weekend staffing was the same or decreased versus weekday staffing, then pooled the mortality rates for studies where staffing levels were the same (versus weekday) and also separately pooled studies where staffing levels were decreased (versus weekday). Data were managed with Stata 13 (Stata Statistical Software: Release 13; StataCorp. 2013, College Station, TX) and R, and all

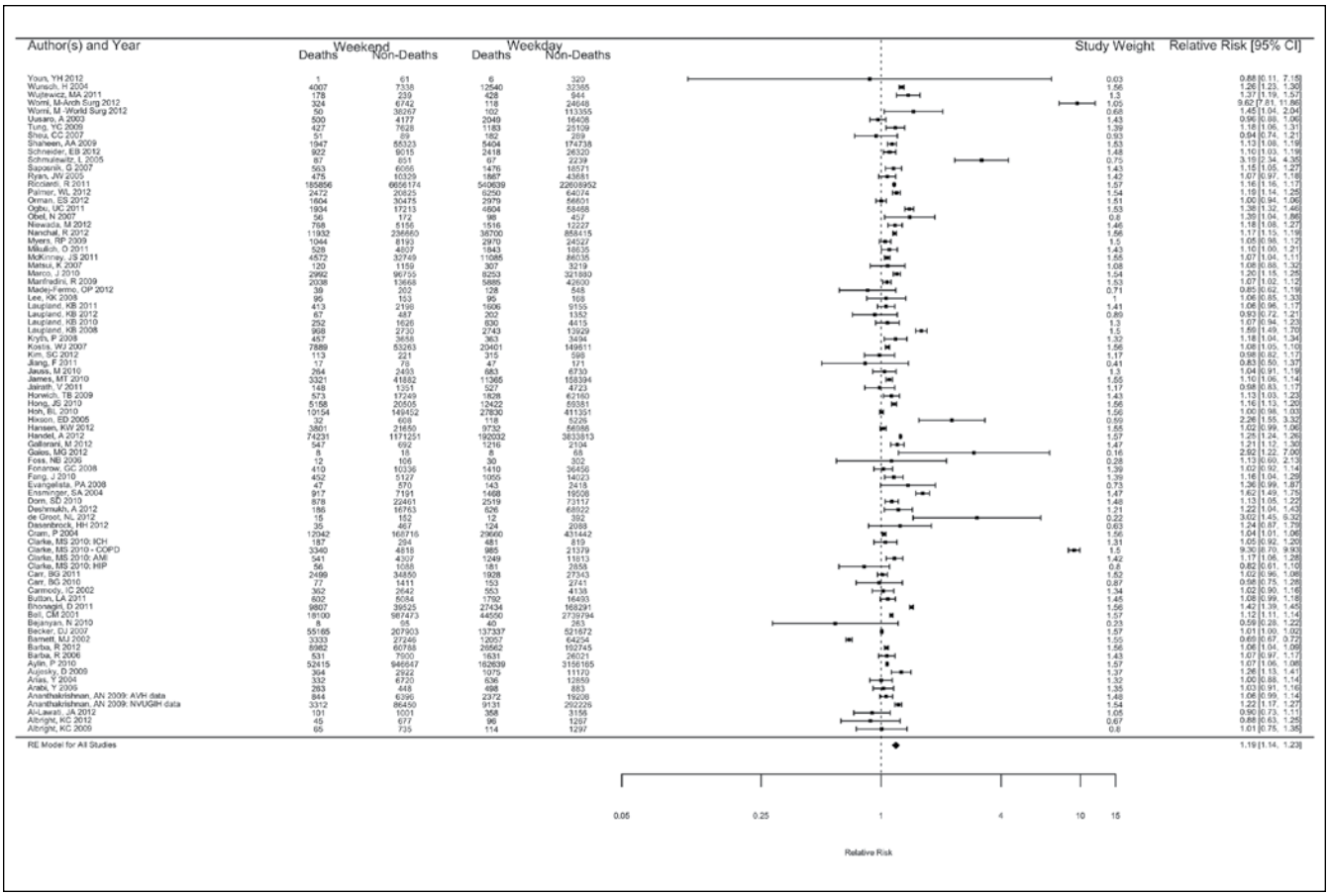

FIG 2. Pooled estimate for mortality between weekend and weekday patients. Patients who were admitted or cared for on the weekends had a significantly higher relative risk (RR) for mortality compared to those admitted or cared for on weekdays (RR, 1.19; 95% confidence interval, 1.14-1.23).

meta-analyses were performed with the metafor package in R.[15] Pooled estimated are presented as RR (95% confidence intervals [CI]).

RESULTS

A literature search retrieved a total of 594 unique citations. A review of the bibliographic references yielded an additional 20 articles. Upon evaluation, 97 studies (N = 51,114,109 patients) met inclusion criteria (Figure 1). The articles were published between 2001–2012; the kappa statistic comparing interrater reliability in the selection of articles was 0.86. Supplementary Tables 1 and 2 present a summary of study characteristics and outcomes of the accepted articles. A summary of accepted studies is in Supplementary Table 1. When summing the total number of subjects across all 97 articles, 76% were classified as weekday and 24% were weekend patients.

Weekend Admission/Inpatient Status and Mortality

The definition of the weekend varied among the included studies. The weekend time period was delineated as Friday midnight to Sunday midnight in 66% (65/99) of the studies. The remaining studies typically defined the weekend to be between Friday evening and Monday morning although studies from the Middle East generally defined the weekend as Wednesday/Thursday through Saturday. The definition of mortality also varied among researchers with most studies describing death rate as hospital inpatient mortality although some studies also examined multiple definitions of mortality (eg, 30-day all-cause mortality and hospital inpatient mortality). Not all studies provided a specific timeframe for mortality.

There were 522,801 weekend deaths (of 12,279,385 weekend patients, or 4.26%) and 1,440,685 weekday deaths (of 39,834,724 weekday patients, or 3.62%). Patients admitted on the weekends had a significantly higher overall mortality compared to those during the weekday. The risk of mortality was 19% greater for weekend admissions versus weekday admissions (RR = 1.19; 95% CI, 1.14-1.23; I^2 = 99%; Figure 2). This same comparison, expressed as a difference in proportions (risk difference) is 0.014 (95% CI, 0.013-0.016). While this difference may seem minor, this translates into 14 more deaths per 1000 patients admitted on weekends compared with those admitted during the week.

Fifty studies did not report a specific time frame for deaths. When a specific time frame for death was reported, the most common reported time frame was 30 days (n = 15 studies) and risk of mortality at 30 days still was higher for weekends

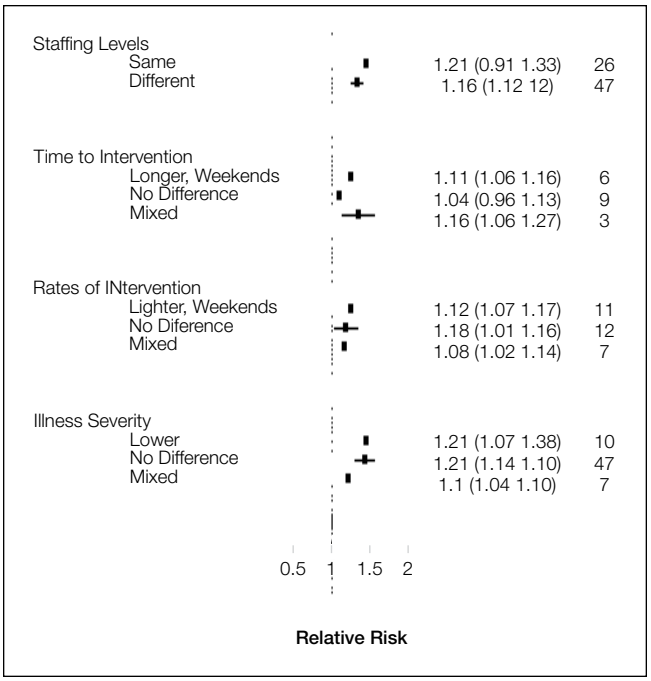

FIG 3. Subgroup analysis between weekend and weekday patients for staffing levels, time to intervention or procedures, rate of intervention or procedures, and illness severity (as defined by the original manuscripts). Patients admitted on the weekends consistently had higher mortality than those admitted during the week.

(RR = 1.07; 95% CI,1.03-1.12; I^2 = 90%). When we restricted the analysis to the studies that specified any timeframe for mortality (n = 49 studies), the risk of mortality was still significantly higher for weekends (RR = 1.12; 95% CI,1.09-1.15; I^2 = 95%).

Weekend Effect Factors

We also performed subgroup analyses to investigate the overall weekend effect by hospital level factors (weekend staffing, procedure rates and delays, illness severity). Complete data were not available for all studies (staffing levels = 73 studies, time to intervention = 18 studies, rate of intervention = 30 studies, illness severity = 64 studies). Patients admitted on the weekends consistently had higher mortality than those admitted during the week, regardless of the levels of weekend/weekday differences in staffing, procedure rates and delays, illness severity (Figure 3). Analysis of studies that included staffing data for weekends revealed that decreased staffing levels on the weekends was associated with a higher mortality for weekend patients (RR = 1.16; 95% CI, 1.12-1.20; I^2 = 99%; Figure 3). There was no difference in mortality for weekend patients when staffing was similar to that for the weekdays (RR = 1.21; 95% CI, 0.91-1.63; I^2 = 99%).

Analysis for weekend data revealed that longer times to interventions on weekends were associated with significantly higher mortality rates (RR = 1.11; 95% CI, 1.08-1.15; I^2 = 0%; Figure 3). When there were no delays to weekend procedure/interventions, there was no difference in mortality between weekend and weekday procedures/interventions (RR = 1.04; 95% CI, 0.96-1.13; I^2 = 55%; Figure 3). Some articles included several procedures with "mixed" results (some procedures were "positive," while other were "negative" for increased mortality). In studies that showed a mixed result for time to intervention, there was a significant increase in mortality (RR = 1.16; 95% CI, 1.06-1.27; I^2 = 42%) for weekend patients (Figure 3).

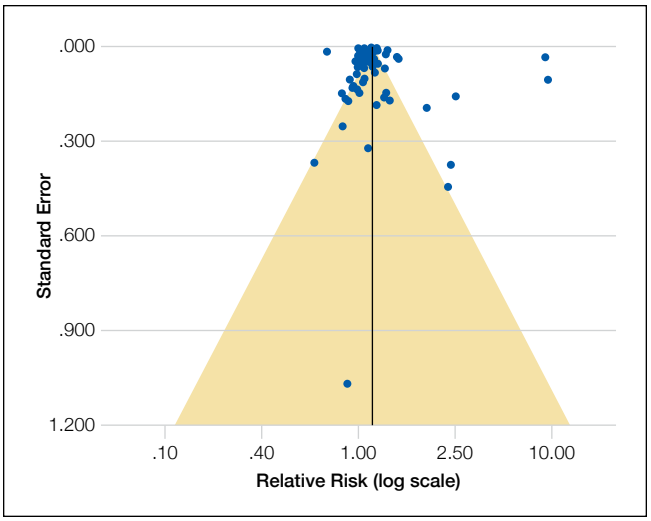

FIG 4. Funnel plot.

Analyses showed a higher mortality rate on the weekends regardless of whether the rate of intervention/procedures was lower (RR=1.12; 95% CI, 1.07-1.17; I^2 = 79%) or the same between weekend and weekdays (RR = 1.08; 95% CI, 1.01-1.16; I^2 = 90%; Figure 3). Analyses showed a higher mortality rate on the weekends regardless of whether the illness severity was higher on the weekends (RR = 1.21; 95% CI, 1.07-1.38; I^2 = 99%) or the same (RR = 1.21; 95% CI, 1.14-1.28; I^2 = 99%) versus that for weekday patients (Figure 3). An inverse funnel plot for publication bias is shown in Figure 4.

DISCUSSION

We have presented one of the first meta-analyses to examine the mortality rate for hospital inpatients admitted during the weekend compared with those admitted during the workweek. We found that patients admitted on the weekends had a significantly higher overall mortality (RR = 1.19; 95% CI, 1.14-1.23; risk difference = 0.014; 95% CI, 0.013-0.016). This association was not modified by differences in weekday and weekend staffing patterns, and other hospital characteristics. Previous systematic reviews have been exclusive to the intensive care unit setting[16] or did not specifically examine weekend mortality, which was a component of "off-shift" and/or "after-hours" care.[17]

These findings should be placed in the context of the recently published literature.[18,19] A meta-analysis of cohort studies found that off-hour admission was associated with increased mortality for 28 diseases although the associations

varied considerably for different diseases.[18] Likewise, a meta-analysis of 21 cohort studies noted that off-hour presentation for patients with acute ischemic stroke was associated with significantly higher short-term mortality.[19] Our results of increased weekend mortality corroborate that found in these two meta-analyses. However, our study differs in that we specifically examined only weekend mortality and did not include after-hours care on weekdays, which was included in the off-hour mortality in the other meta-analyses.[18,19]

Differences in healthcare worker staffing between weekends and weekdays have been proposed to contribute to the observed increase in mortality.[7,16,20] Data indicate that lower levels of nursing are associated with increased mortality.[10,21-23] The presence of less experienced and/or fewer physician specialists may contribute to increases in mortality.[24-26] Fewer or less experienced staff during weekends may contribute to inadequacies in patient handovers and/or handoffs, delays in patient assessment and/or interventions, and overall continuity of care for newly admitted patients.[27-33]

Our data show little conclusive evidence that the weekend mortality versus weekday mortality vary by staffing level differences. While the estimated RR of mortality differs in magnitude for facilities with no difference in weekend and weekday staffing versus those that have a difference in staffing levels, both estimate an increased mortality on weekends, and the difference in these effects is not statistically significant. It should be noted that there was no difference in mortality for weekend (versus weekday) patients where there was no difference between weekend and weekday staffing; these studies were typically in high acuity units or centers where the general expectation is for 24/7/365 uniform staffing coverage.

A decrease in the use of interventions and/or procedures on weekends has been suggested to contribute to increases in mortality for patients admitted on the weekends.[34] Several studies have associated lower weekend rates to higher mortality for a variety of interventions,[13,35-37] although some other studies have suggested that lower procedure rates on weekends have no effect on mortality.[38-40] Lower diagnostic procedure weekend rates linked to higher mortality rates may exacerbate underlying healthcare disparities.[41] Our results do not conclusively show that a decrease rate of intervention and/or procedures for weekends patients is associated with a higher risk of mortality for weekends compared to weekdays.

Delays in intervention and/or procedure on weekends have also been suggested to contribute to increases in mortality.[34,42] Similar to that seen with lower rates of diagnostic or therapeutic intervention and/or procedure performed on weekends, delays in potentially critical intervention and/or procedures might ultimately manifest as an increase in mortality.[43] Patients admitted to the hospital on weekends and requiring an early procedure were less likely to receive it within 2 days of admission.[42] Several studies have shown an association between delays in diagnostic or therapeutic intervention and/or procedure on weekends to a higher hospital inpatient mortality[35,42,44,45]; however, some data suggested that a delay in time to procedure on weekends may not always be associated with increased mortality.[46] Depending on the procedure, there may be a threshold below which the effect of reducing delay times will have no effect on mortality rates.[47,48]

Patients admitted on the weekends may be different (in the severity of illness and/or comorbidities) than those admitted during the workweek and these potential differences may be a factor for increases in mortality for weekend patients. Whether there is a selection bias for weekend versus weekday patients is not clear.[34] This is a complex issue as there is significant heterogeneity in patient case mix depending on the specific disease or condition studied. For instance, one would expect that weekend trauma patients would be different than those seen during the regular workweek.[49] Some large scale studies suggest that weekend patients may not be more sick than weekday patients and that any increase in weekend mortality is probably not due to factors such as severity of illness.[1,7] Although we were unable to determine if there was an overall difference in illness severity between weekend and weekday patients due to the wide variety of assessments used for illness severity, our results showed statistically comparable higher mortality rate on the weekends regardless of whether the illness severity was higher, the same, or mixed between weekend and weekday patients, suggesting that general illness severity per se may not be as important as the weekend effect on mortality; however, illness severity may still have an important effect on mortality for more specific subgroups (eg, trauma).[49]

There are several implications of our results. We found a mean increased RR mortality of approximately 19% for patients admitted on the weekends, a number similar to one of the largest published observational studies containing almost 5 million subjects.[2] Even if we took a more conservative estimate of 10% increased risk of weekend mortality, this would be equivalent to an excess of 25,000 preventable deaths per year. If the weekend effect were to be placed in context of a public health issue, the weekend effect would be the number 8 cause of death below the 29,000 deaths due to gun violence, but above the 20,000 deaths resulting from sexual behavior (sexual transmitted diseases) in 2000.[3, 50,51] Although our data suggest that staffing shortfalls and decreases or delays for procedures on weekends may be associated with an increased mortality for patients admitted on the weekends, further large-scale studies are needed to confirm these findings. Increasing nurse and physician staffing levels and skill mix to cover any potential shortfall on weekends may be expensive, although theoretically, there may be savings accrued from reduced adverse events and shorter length of stay.[26,52] Changes to weekend care might only benefit daytime hospitalizations because some studies have shown increased mortality during nighttime regardless of weekend or weekday admission.[53]

Several methodologic points in our study need to be clarified. We excluded many studies which examined the relationship of off-hours or after-hours admissions and mortality as off-hours studies typically combined weekend and after-hours

weekday data. Some studies suggest that off-hour admission may be associated with increased mortality and delays in time for critical procedures during off-hours.[18,19] This is a complex topic, but it is clear that the risks of hospitalization vary not just by the day of the week but also by time of the day.[54] The use of meta-analyses of nonrandomized trials has been somewhat controversial,[55,56] and there may be significant bias or confounding in the pooling of highly varied studies. It is important to keep in mind that there are very different definitions of weekends, populations studied, and measures of mortality rates, even as the pooled statistic suggests a homogeneity among the studies that does not exist.

There are several limitations to our study. Our systematic review may be seen as limited as we included only English language papers. In addition, we did not search nontraditional sources and abstracts. We accepted the definition of a weekend as defined by the original study, which resulted in varied definitions of weekend time period and mortality. There was a lack of specific data on staffing patterns and procedures in many studies, particularly those using databases. We were not able to further subdivide our analysis by admitting service. We were not able to undertake a subgroup analysis by country or continent, which may have implications on the effect of different healthcare systems on healthcare quality. It is unclear whether correlations in our study are a direct consequence of poorer weekend care or are the result of other unknown or unexamined differences between weekend and weekday patient populations.[34,57] For instance, there may be other global factors (higher rates of medical errors, higher hospital volumes) which may not be specifically related to weekend care and therefore not been accounted for in many of the studies we examined.[10,27,58-61] There may be potential bias of patient phenotypes (are weekend patients different than weekday patients?) admitted on the weekend. Holidays were included in the weekend data and it is not clear how this would affect our findings as some data suggest that there is a significantly higher mortality rate on holidays (versus weekends or weekdays),[61] while other data do not.[62] There was no universal definition for the timeframe for a weekend and as such, we had to rely on the original article for their determination and definition of weekend versus weekday death.

In summary, our meta-analysis suggests that hospital inpatients admitted during the weekend have a significantly increased mortality compared with those admitted on weekday. While none of our subgroup analyses showed strong evidence on effect modification, the interpretation of these results is hampered by the relatively small number of studies. Further research should be directed to determine the presence of causality between various factors purported to affect mortality and it is possible that we ultimately find that the weekend effect may exist for some but not all patients.

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Hospital Medicine Point of Care Ultrasound Credentialing: An Example Protocol

Benji K. Mathews, MD[1,2*], Michael Zwank, MD, RDMS[2,3]

[1]Department of Hospital Medicine, HealthPartners, University of Minnesota Medical School, Minneapolis, Minnesota; [2]University of Minnesota Medical School, Minneapolis, Minnesota; [3]Department of Emergency Medicine, Regions Hospital, St. Paul, Minnesota.

Though the use of point-of-care ultrasound (POCUS) has increased over the last decade, formal hospital credentialing for POCUS may still be a challenge for hospitalists. This document details the Hospital Medicine Department Ultrasound Credentialing Policy from Regions Hospital, which is part of the HealthPartners organization in Saint Paul, Minnesota.

National organizations from internal medicine and hospital medicine (HM) have not published recommended guidelines for POCUS credentialing. Revised guidelines for POCUS have been published by the American College of Emergency Physicians, though these are not likely intended to guide hospitalists when working with credentialing committees and medical boards.

This document describes the scope of ultrasound in HM and our training, credentialing, and quality assurance program. This report is intended to be used as a guide for hospitalists as they work with their own credentialing committees and will require modification for each institution. However, the overall process described here should assist in the establishment of POCUS at various institutions. *Journal of Hospital Medicine* 2017;12:767-772. © 2017 Society of Hospital Medicine

Ultrasound has been used for decades by radiology, obstetrics-gynecology, and cardiology departments within a comprehensive paradigm in which a physician enters an order, then a trained sonographer performs the study, followed by a physician evaluating and interpreting the images.[1] Unlike the traditional comprehensive paradigm, point-of-care ultrasound (POCUS) is a focused study that is both performed and interpreted by the bedside provider.[2] POCUS has been demonstrated to improve diagnosis and clinical management in multiple studies.[3-15]

The scope of practice in POCUS differs by specialty, as POCUS is done to achieve specific procedural aims (eg, direct the needle to the correct location) or answer focused questions (eg, does the patient have a distended bladder?) related to the specialty. POCUS in hospital medicine (HM) provides immediate answers, without the delay and potential risk of transportation to other hospital areas. It may be used to diagnose pleural effusion, pneumonia, hydronephrosis, heart failure, deep vein thrombosis, and many other pathologies.[5-15] It is important to understand that POCUS performed by HM is a limited study and is not a substitute for more complete ultrasound examinations conducted in the radiology suite or in the echocardiography lab.

Address for correspondence and reprint requests: Benji K. Mathews, MD, FACP, CLHM Department of Hospital Medicine, HealthPartners, Department of Hospital Medicine, Regions Hospital, 640 Jackson Street, Mail Stop 11109E, St. Paul, MN 55101; Telephone: 651-254-9555; Fax: 651-254-9673; E-mail: benji@umn.edu

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POCUS should not be used exclusively in medical decision making, but rather in conjunction with the greater clinical context of each patient, building on established principles of diagnosis and management.

DEFINITIONS

- Credentialing: An umbrella term, which incorporates licensure, education, and certification.
- Privileging: Used to define the scope authorized for a provider by a healthcare organization based on an evaluation of the individual's credentials and performance.
- Competency: An observable ability of a provider, integrating multiple components, such as knowledge and skills. Since competencies are observable, they can be measured and assessed to ensure their acquisition.
- Certification: The process by which an association grants recognition to a provider who has met certain predetermined qualifications specified by the association. Competence is distinguished from certification, which is defined as the process by which competence is recognized by an external agency.

All of the above mechanisms work together to provide the highest quality of reliability that a practitioner is providing safe, competent care.[16-18]

STATEMENTS FROM MAJOR SPECIALTY SOCIETIES

Acknowledging that there are no published guidelines in the realm of HM POCUS, the development of the credentialing process at our institution is consistent with published guidelines by Emergency Medicine societies (the most established physician users of POCUS) and the American Medical Association (AMA).[19-21]

The use of emergency ultrasound by physicians in the emergency department is endorsed by the American College

TABLE. Hospital Medicine Portfolio Requirements

Cardiac Study (20 studies with the following images per study)[22,54-76]
Total: 100 images 1. Parasternal long axis view 2. Parasternal short axis view 3. Apical four-chamber view 4. Subcostal long axis view 5. Inferior vena cava longitudinal view
Lung/Pleural Study (5 studies with the following images per study)[43-53]
Total: 20 images 1. Pleural effusion (any size) 2. Sliding lung with A-lines 3. Consolidation 4. B-lines
Abdominal Study (5 studies with the following images per study)[27-34]
Total: 20 images 1. Left kidney longitudinal view with splenorenal space 2. Right kidney longitudinal view with hepatorenal recess 3. Abdominal aorta longitudinal view 4. Bladder transverse view
Vascular Diagnostic DVT Study (3 studies with the following images per study; include right and left legs)[35-42]
Total: 24 images 1. Right common femoral vein with compression 2. Left common femoral vein with compression 3. Right common femoral vein at saphenous intake with compression 4. Left common femoral vein at saphenous intake with compression 5. Right superficial femoral vein with compression 6. Left superficial femoral vein with compression 7. Right popliteal vein with compression 8. Left popliteal vein with compression

Adapted from CHEST Critical Care Ultrasonography Program[18,86]
NOTE: Abbreviation: DVT, deep vein thrombosis.

of Emergency Physicians (ACEP).[19] ACEP, along with the Society of Academic Emergency Medicine (SAEM), recommends that training in the performance and interpretation of ultrasound imaging be included during residency.[20] ACEP and SAEM add that the availability of equivalent training should be made available to practicing physicians. The American Society of Echocardiography has supported the use of POCUS and sees this modality as part of the continuum of care.[23,24]

The AMA has also recognized that POCUS is within the scope of practice of trained physicians.[22] The AMA further recommended hospital staff create their own criteria for granting ultrasound privileges based on the background and training of the physician and in accordance with the standards set within specific specialties.[22,23]

LOCAL POLICY AND PROCEDURE

The provision of clinical privileges in HM is governed by the rules and regulations of the department and institution for which privileges are sought. In detailing our policies and procedures above, we intend to provide an example for HM departments at other institutions that are attempting to create a POCUS credentialing program.

An interdisciplinary approach was created by our institution to address training, competency, and ongoing quality assurance (QA) concerns due to the increasing popularity of POCUS and variability in its use. We developed a hospital-wide POCUS committee with, among others, members from HM, emergency medicine, critical care, radiology, and cardiology, with a charter to standardize POCUS across departments. After review of the literature,[16-18, 20, 21, 23-74] baseline training requirements were established for credentialing and developing a unified delineation of privileges for hospital-wide POCUS. The data support the use of a variety of assessments to ensure a provider has developed competence (portfolio development, knowledge-based examination, skills-based assessment, ongoing QA process). The POCUS committee identified which exams could be performed at bedside for credentialed providers, delineated imaging requirements for each exam, and set up the information technology infrastructure to support ordering and reporting through electronic health records (EHR). While the POCUS committee delineated this process for all hospital providers, we will focus our discussion on the credentialing policy and procedure in HM.

STEP 1: PATHWAY TO POCUS CREDENTIALING IN HM: COMPLETE MINIMAL FORMAL REQUIREMENTS

The credentialing requirements at our institution include one of the the following basic education pathways and minimal formal training:

Residency/Fellowship Based Pathway

Completed training in an Accreditation Council for Graduate Medical Education–approved program that provided opportunities for 20 hours of POCUS training with at least 6 hours of hands-on ultrasound scanning, 5 proctored limited cardiac ultrasound cases and portfolio development.

Practice Based Pathway

Completed 20 hours of POCUS continuing medical education (CME) with at least 6 hours of hands-on ultrasound scanning and has completed 5 proctored limited cardiac ultrasound cases (as part of CME).

The majority of HM providers had little formal residency training in POCUS, so a training program needed to be developed. Our training program, modeled after the American College of Chest Physicians' CHEST certificate of completion,[86] utilizes didactic training, hands-on instruction, and portfolio development that fulfills the minimal formal requirements in the practice-based pathway.

STEP 2: PATHWAY TO POCUS CREDENTIALING IN HM: COMPLETE PORTFOLIO AND FINAL ASSESSMENTS (KNOWLEDGE AND SKILLS–BASED)

After satisfactory completion of the minimal formal training, applicants need to provide documentation of a set number of cases. To aid this requirement, our HM department developed the portfolio guidelines in the Table. These are

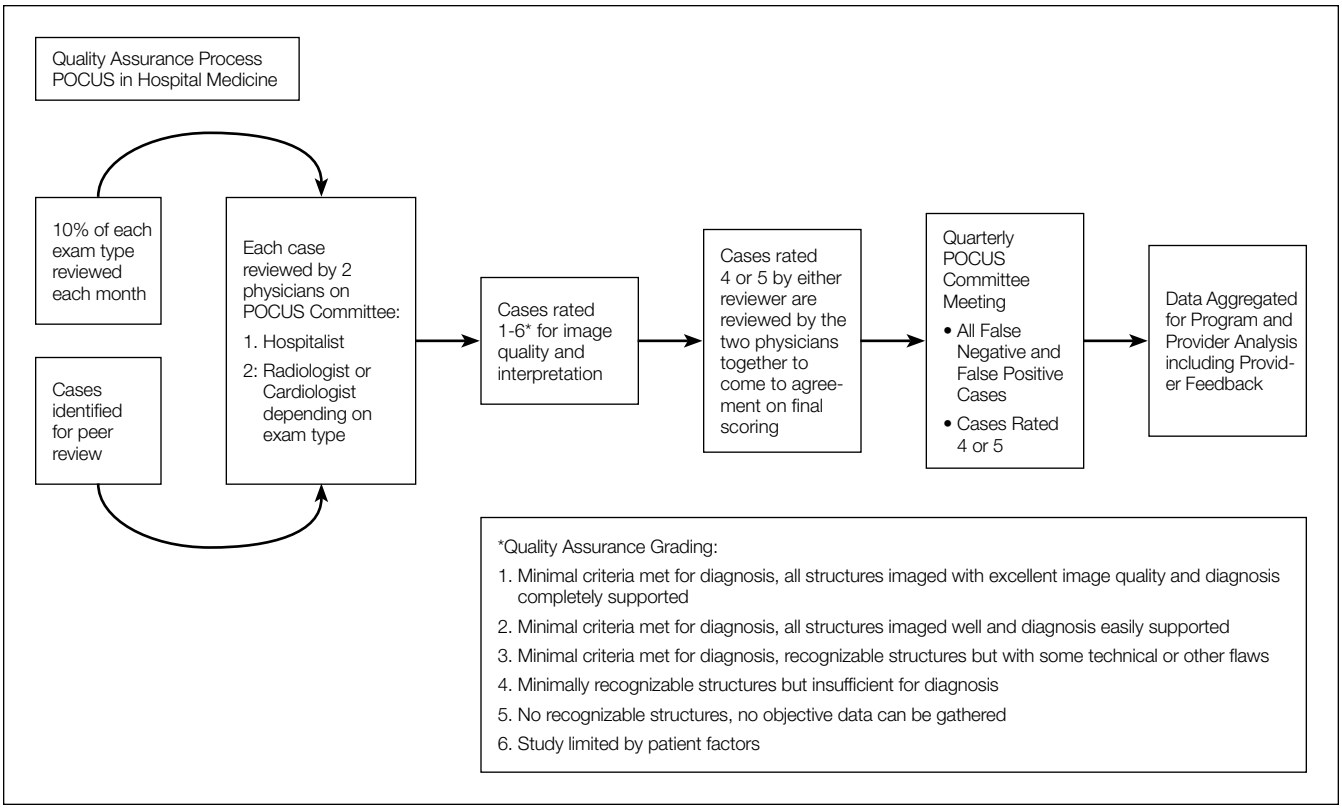

FIG. Quality Assurance process. NOTE: Abbreviation: POCUS, point-of-care ultrasound.

minimum requirements, and because of the varying training curves of learning,[76-80] 1 hospitalist may need to submit 300 files for review to meet the standards, while another may need to submit 500 files. Submissions are not accepted unless they yield high-quality video files with meticulous attention to gain, depth, and appropriate topographic planes. The portfolio development monitors hospitalists' progression during their deliberate practice, providing objective assessments, feedback, and mentorship.[81,82]

A final knowledge exam with case-based image interpretation and hands-on examination is also provided. The passing score for the written examination is 85% and was based on the Angoff methodology.[75] Providers who meet these requirements are then able to apply for POCUS credentialing in HM. Providers who do not pass the final assessments are required to participate in further training before they reattempt the assessments. There is uniformity in training outcomes but diversity in training time for POCUS providers.

Candidates who complete the portfolio and satisfactorily pass the final assessments are credentialed after review by the POCUS committee. Credentialed physicians are then able to perform POCUS and to integrate the findings into patient care.

MAINTENANCE OF CREDENTIALS

Documentation

After credentialing is obtained, all POCUS studies used in patient care are included in the EHR following a clearly defined workflow. The study is ordered through the EHR and is retrieved wirelessly on the ultrasound machine. After performing the ultrasound, all images are wirelessly transferred to the radiology Picture Archiving and Communication System server. Standardized text reports are used to distinguish focused POCUS from traditional diagnostic ultrasound studies. Documentation is optimized using electronic drop-down menus for documenting ultrasound findings in the EHR.

Minimum Number of Examinations

Maintenance of credentials will require that each hospitalist perform 10 documented ultrasounds per year for each cardiac and noncardiac application for which credentials are requested. If these numbers are not met, then all the studies performed during the previous year will be reviewed by the ultrasound committee, and providers will be provided with opportunities to meet the minimum benchmark (supervised scanning sessions).

Quality Assurance

Establishing scope of practice, developing curricula, and credentialing criteria are important steps toward assuring provider competence.[16,17,22,74] To be confident that providers are using POCUS appropriately, there must also be a development of standards of periodic assessment that encompass both examination performance and interpretation. The objective of a QA process is to evaluate the POCUS cases for technical competence and the interpretations for clinical accuracy, and

to provide feedback to improve performance of providers.

QA is maintained through the interdisciplinary POCUS committee and is described in the Figure.

After initial credentialing, continued QA of HM POCUS is done for a proportion of ongoing exams (10% as per recommendations by ACEP) to document continued competency.[2] Credentialed POCUS providers perform and document their exam and interpretations. Ultrasound interpretations are reviewed by the POCUS committee (every case by 2 physicians, 1 hospitalist, and 1 radiologist or cardiologist depending on the study type) at appropriate intervals based on volume (at minimum, quarterly). A standardized review form is used to grade images and interpretations. This is the same general rubric used with the portfolio for initial credentialing. Each case is scored on a scale of 1 to 6, with 1 representing high image quality and support for diagnosis and 6 representing studies limited by patient factors. All scores rated 4 or 5 are reviewed at the larger quarterly POCUS committee meetings. For any provider scoring a 4 or 5, the ultrasound committee will recommend a focused professional practice evaluation as it pertains to POCUS. The committee will also make recommendations on a physician's continued privileges to the department leaders.[83]

BILLING

Coding, billing, and reimbursement for focused ultrasound has been supported through the AMA Physicians' Current Procedural Terminology (CPT) 2011 codes, which includes CPT code modifiers for POCUS.[84] There are significant costs associated with building a HM ultrasound program, including the education of hospitalists, ultrasound equipment purchase and maintenance, as well as image archiving and QA. The development of a HM ultrasound billing program can help justify and fund these costs.[19,85]

To appropriately bill for POCUS, permanently retrievable images and an interpretation document need to be available for review. HM coders are instructed to only bill if both components are available. Because most insurers will not pay for 2 of the same type of study performed within a 24-hour period, coders do not bill for ultrasounds when a comprehensive ultrasound of the same body region is performed within a 24-hour period. The workflow that we have developed, including ordering, performing, and documenting, allows for easy coding and billing.

BARRIERS AND LIMITATIONS

While POCUS has a well-established literature base in other specialties like emergency medicine, it has been a relatively recent addition to the HM specialty. As such, there exists a paucity of evidence-based medicine to support its use of POCUS in HM. While it is tempting to extrapolate from the literature of other specialties, this may not be a valid approach.

Training curves in which novice users of ultrasound become competent in specific applications are incompletely understood. Little research describes the rate of progression of learners in ultrasound towards competency. We have recently started the QA process and hope that the data will further guide feedback to the process.

Additionally, with the portfolios, the raters' expertise may not be stable (develops through experience). We aim to mitigate this by having a group of raters reviewing each file, particularly if there is a question about if a submission is of high image quality. A notable barrier that groups face is support from their leadership regarding POCUS. Our group has had support from the chief medical officer who helped mandate the development of POCUS standards.

LESSONS LEARNED

We have developed a robust collaborative HM POCUS program. We have noted challenges in motivating all providers to work through this protocol. Development of a POCUS program takes dedicated time, and without a champion, it is at risk for failing. HM departments would be advised to seek out willing collaborators at their institutions. We have seen that it is useful to partner with some experienced emergency medicine providers. Additionally, portfolio development and feedback has been key to demonstrating growth in image acquisition. Deliberate longitudinal practice with feedback and successive refinements with POCUS obtain the highest yield towards competency. We hope our QA data will provide further feedback into the credentialing policy and procedure.

SUMMARY

It is important that POCUS users work together to recognize its potential and limitations, teach current and future care providers' best practices, and create an infrastructure that maximizes quality of care while minimizing patient risk.

We are hopeful that this document will prove beneficial to other HM departments in the development of successful POCUS programs. We feel that it is important to make available to other HM departments a concise protocol that has successfully passed through the credentialing process at a large tertiary care medical system.

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A Video Is Worth a Thousand Words

Kara Bischoff MD*, Wendy Anderson MD, Steve Z. Pantilat MD

Department of Medicine, University of California, San Francisco, San Francisco, California.

There is no doubt about the importance of assessing, documenting, and honoring patient wishes regarding care. For hospitalized patients, code status is a critical treatment preference to document given that the need for cardiopulmonary resuscitation (CPR) arises suddenly, outcomes are often poor, and the default is for patients to receive the treatment unless they actively decline it. Hospitalists are expected to document code status for every hospitalized patient, but admission code status conversations are often brief—and that might be all right. A code status discussion for a 70-year-old man with no chronic medical problems and excellent functional status who has been admitted for pain after a motor vehicle accident may require only an introduction to the concept of advance care planning, the importance of having a surrogate, and confirmation of full code status. On the other hand, a 45-year-old woman with metastatic pancreatic cancer would likely benefit from a family meeting in which the hospitalist could review her disease course and prognosis, assess her values and priorities in the context of her advanced illness, make treatment recommendations—including code status—that are consistent with her values, and elicit questions.[1,2] We need to free up hospitalists from spending time discussing code status with every patient so that they can spend more time in quality goals of care discussions with seriously ill patients. The paradigm of the one doctor—one patient admission code status conversation for every patient is no longer realistic.

As reported by Merino and colleagues in this issue of *JHM*, video decision aids about CPR for hospitalized patients can offer an innovative solution to determining code status for hospitalized patients.[3] The authors conducted a prospective, randomized controlled trial, which enrolled older adults admitted to the hospital medicine service at the Veteran's Administration (VA) Hospital in Minneapolis. Participants (N = 119) were randomized to usual care or to watch a 6-minute video that explained code status options, used a mannequin to illustrate a mock code, and provided information about potential complications and survival rates. Patients who watched the video were more likely to choose do not resuscitate/do not intubate status, with a large effect size (56% in the intervention group vs. 17% in the control group, $P < 0.00001$).

Address for correspondence and print requests: Kara Bischoff, MD, UCSF Department of Medicine, Box 0131, 533 Parnassus Ave, San Francisco, CA 94143; Telephone: 415-606-1041; Fax: 415-476-5020; E-mail: Kara.Bischoff@ucsf.edu

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This study adds to a growing body of literature about this powerful modality to assist with advanced care planning. Over the past 10 years, studies—conducted primarily by Volandes, El-Jawahri, and colleagues—have demonstrated how video decision aids impact the care that patients want in the setting of cancer, heart failure, serious illness with short prognosis, and future dementia.[4-9] This literature has also shown that video decision aids can increase patients' knowledge about CPR and increase the stability of decisions over time. Further, video decision aids have been well accepted by patients, who report that they would recommended such videos to others. This body of evidence underscores the potential of video decision aids to improve concordance between patient preferences and care provided, which is key given the longstanding and widespread concern about patients receiving care that is inconsistent with their values at the end of life.[10] In short, video decision aids work.

Merino and colleagues are the first to examine the use of a video decision aid about code status in a general population of older adults on a hospital medicine service and the second to integrate such a video into usual inpatient care, which are important advancements.[2,3] There are several issues that warrant further consideration prior to widely disseminating such a video, however. As the authors note, the participants in this VA study were overwhelmingly white men and their average age was 75. Further, the authors found a nonsignificant trend towards patients in the intervention group having less trust that "my doctors and healthcare team want what is best for me" (76% in the intervention group vs. 93% in the control group; $P = 0.083$). Decision making about life-sustaining therapies and reactions to communication about serious illness are heavily influenced by cultural and socioeconomic factors, including health literacy.[11] It will be important to seek feedback from a diverse group of patients and families to ensure that the video decision aid is interpreted accurately, renders decisions that are consistent with patients' values, and does not negatively impact the clinician-patient relationship.[12] Additionally, as the above cases illustrate, code status discussions should be tailored to patient factors, including illness severity and point in the disease course. Hospitalists will ultimately benefit from having access to multiple different videos about a range of advance care planning topics that can be used when appropriate.

In addition to selecting the right video for the right patient, the next challenge for hospitalists and health systems will be how to implement them within real-world clinical care and a broader approach to advance care planning. There are technical and logistical challenges to displaying

videos in hospital rooms, and more significant challenges in ensuring timely follow-up discussions, communication of patients' dynamic care preferences to their surrogates, changes to inpatient orders, documentation in the electronic medical record where it can be easily found in the future, and completion of advance directives and Physician Orders for Life Sustaining Treatment forms to communicate patients' goals of care beyond the hospital and health system. Each of these steps is critical and is supported through videos and activities in the free, patient-facing, PREPARE web-based tool (https://www.prepareforyourcare.org/).[2,13,14]

The ubiquitous presence of videos in our lives speaks to their power to engage and affect us. Video decision aids provide detailed explanations and vivid images that convey more than words can alone. While there is more work to be done to ensure videos are appropriate for all hospitalized patients and support rather than detract from patient-doctor relationships, this study and others like it show that video decision aids are potent tools to promote better decision-making and higher value, more efficient care.

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Certification of Point-of-Care Ultrasound Competency

Nilam J. Soni, MD, MS[1,2*], David M. Tierney, MD[3], Trevor P. Jensen, MD, MS[4], Brian P. Lucas, MD, MS[5,6]

[1]Division of General & Hospital Medicine, The University of Texas School of Medicine at San Antonio, San Antonio, Texas; [2]Section of Hospital Medicine, South Texas Veterans Health Care System, San Antonio, Texas; [3]Abbott Northwestern Hospital, Department of Medical Education, Minneapolis, Minnesota; [4]Division of Hospital Medicine, Department of Medicine, University of California San Francisco, San Francisco, California; [5]Medicine Service, White River Junction VA Medical Center, White River Junction, Vermont; [6]Geisel School of Medicine at Dartmouth College, Hanover, New Hampshire.

Any conversation about point-of-care ultrasound (POCUS) inevitably brings up discussion about credentialing, privileging, and certification. While credentialing and privileging are institution-specific processes, competency certification can be extramural through a national board or intramural through an institutional process.

Currently, no broadly accepted national board certification for POCUS exists; however, some specialty boards, such as emergency medicine, already include competency in POCUS. Thus, many institutions grant POCUS privileges to emergency medicine physicians based solely on their national board certification. In contrast, most hospitalists are certified by the American Board of Internal Medicine, which does not include competency in POCUS. Some hospitalists have pursued extramural certificate programs offered by professional organizations, such as the American College of Chest Physicians. The currently available extramural certificate programs can certify basic competency in POCUS knowledge and skills. But none of them can deem a provider competent in POCUS, which requires mastery of knowledge, image acquisition, image interpretation, and clinical integration (Figure). Image acquisition and interpretation skills are learned at varying rates. Those skills, followed by an understanding of how to integrate POCUS findings into clinical care of patients, are ones that cannot be acquired after a weekend training course.[1]

Some institutions have begun to develop intramural certification pathways for POCUS competency in order to grant privileges to hospitalists. In this edition of the *Journal of Hospital Medicine*, Mathews and Zwank[2] describe a multidisciplinary collaboration to provide POCUS training, intramural certification, and quality assurance for hospitalists at one hospital in Minnesota. This model serves as a real-world example of how institutions are addressing the need to certify hospitalists in basic POCUS competency. After engaging stakeholders from radiology, critical care, emergency medicine, and cardiology, institutional standards were developed and hospitalists were assessed for basic POCUS competency. Certification included assessments of hospitalists' knowledge, image acquisition, and image interpretation skills. The model described by Mathews did not assess competency in clinical integration but laid the groundwork for future evaluation of clinical outcomes in the cohort of certified hospitalists.

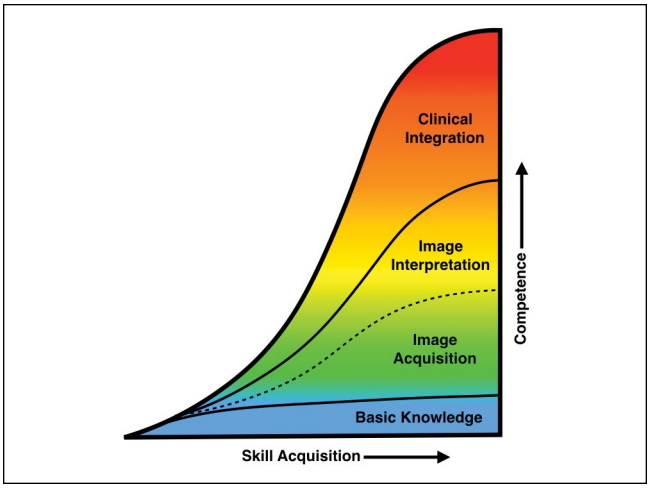

FIG. Competency in point-of-care ultrasound requires mastery of different skills. After gaining basic knowledge of ultrasonography, image acquisition and interpretation skills can be mastered. Clinical integration of ultrasound findings requires baseline competence in clinical medicine.

Although experts may not agree on all aspects of competency in POCUS, most will agree with the basic principles outlined by Mathews and Zwank. Initial certification should be based on training and an initial assessment of competency. Components of training should include ultrasound didactics, mentored hands-on practice, independent hands-on practice, and image interpretation practice. Ongoing certification should be based on quality assurance incorporated with an ongoing assessment of skills. Additionally, most experts will agree that competency can be recognized, and formative and summative assessments that combine a gestalt of provider skills with quantitative scoring systems using checklists are likely the best approach.

The real question is, what is the goal of certification of POCUS competency? Development of an institutional certification process demands substantive resources of the institution and time of the providers. Institutions would have to invest in equipment and staff to operate a full-time certification program, given the large number of providers that

***Address for correspondence and reprint requests:** Nilam J. Soni, MD, MS, 7703 Floyd Curl Drive, MC 7982, San Antonio, TX 78229; Telephone: 210-743-6030; Fax: 210-358-0647; E-mail: sonin@uthscsa.edu

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use POCUS and justify why substantive resources are being dedicated to certify POCUS skills and not others. Providers may be dissuaded from using POCUS if certification requirements are burdensome, which has potential negative consequences, such as reverting back to performing bedside procedures without ultrasound guidance or referring all patients to interventional radiology.

Conceptually, one may speculate that certification is required for providers to bill for POCUS exams, but certification is not required to bill, although institutions may require certification before granting privileges to use POCUS. However, based on the emergency medicine experience, a specialty that has been using POCUS for more than 20 years, billing may not be the main driver of POCUS use. A recent review of 2012 Medicare data revealed that <1% of emergency medicine providers received reimbursement for limited ultrasound exams.[3] Despite the Accreditation Council for Graduate Medical Education (ACGME) requirement for POCUS competency of all graduating emergency medicine residents since 2001 and the increasing POCUS use reported by emergency medicine physicians,[4,5] most emergency medicine physicians are not billing for POCUS exams. Maybe use of POCUS as a "quick look" or extension of the physical examination is more common than previously thought. Although billing for POCUS exams can generate some clinical revenue, the benefits for the healthcare system by expediting care,[6,7] reducing ancillary testing,[8,9] and reducing procedural complications[10,11] likely outweigh the small gains from billing for limited ultrasound exams. As healthcare payment models evolve to reward healthcare systems that achieve good outcomes rather than services rendered, certification for the sole purpose of billing may become obsolete. Furthermore, concerns about billing increasing medical liability from using POCUS are likely overstated because few lawsuits have resulted from missed diagnoses by POCUS, and most lawsuits have been from failure to perform a POCUS exam in a timely manner.[12,13]

Many medical students graduating today have had some training in POCUS[14] and, as this new generation of physicians enters the workforce, they will likely view POCUS as part of their routine bedside evaluation of patients. If POCUS training is integrated into medical school and residency curricula, and national board certification incorporates basic POCUS competency, then most institutions may no longer feel obligated to certify POCUS competency locally, and institutional certification programs, such as the one described by Mathews and Zwank, would become obsolete.

For now, until all providers enter the workforce with basic competency in POCUS and medical culture accepts that ultrasound is a diagnostic tool available to any trained provider, hospitalists may need to provide proof of their competence through intramural or extramural certification. The work of Mathews and Zwank provides an example of how local certification processes can be established. In a future edition of the *Journal of Hospital Medicine*, the Society of Hospital Medicine Point-of-Care Ultrasound Task Force will present a position statement with recommendations for certification of competency in bedside ultrasound-guided procedures.

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Inpatient Thrombophilia Testing: At What Expense?

Lauren A. Heidemann, MD[1,2*], Christopher M. Petrilli, MD[1,2], Geoffrey D. Barnes, MD, MSc[3]

[1]Department of Medicine, Division of Hospitall Medicine, University of Michigan, Ann Arbor, Michigan; [2]VA Ann Arbor Healthcare System, Ann Arbor, Michigan; [3]Department of Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, Michigan.

Thrombotic disorders, such as venous thromboembolism (VTE) and acute ischemic stroke, are highly prevalent,[1] morbid, and anxiety-provoking conditions for patients, their families, and providers.[2] Often, a clear cause for these thrombotic events cannot be found, leading to diagnoses of "cryptogenic stroke" or "idiopathic VTE." In response, many patients and clinicians search for a cause with thrombophilia testing.

However, evaluation for thrombophilia is rarely clinically useful in hospitalized patients. Test results are often inaccurate in the setting of acute thrombosis or active anticoagulation. Even when thrombophilia results are reliable, they seldom alter immediate management of the underlying condition, especially for the inherited forms.[3] An important exception is when there is high clinical suspicion for the antiphospholipid syndrome (APS), because APS test results may affect both short-term and long-term drug choices and international normalized ratio target range. Despite the broad recommendations against routine use of thrombophilia testing (including the Choosing Wisely campaign),[4] patterns and cost of testing for inpatient thrombophilia evaluation have not been well reported.

In this issue of Journal of Hospital Medicine, Cox et al.[5] and Mou et al.[6] retrospectively review the appropriateness and impact of inpatient thrombophilia testing at 2 academic centers. In the report by Mou and colleagues, nearly half of all thrombophilia tests were felt to be inappropriate at an excess cost of over $40,000. Cox and colleagues identified that 77% of patients received 1 or more thrombophilia tests with minimal clinical utility. Perhaps most striking, Cox and colleagues report that management was affected in only 2 of 163 patients (1.2%) that received thrombophilia testing; both had cryptogenic stroke and both were started on anticoagulation after testing positive for multiple coagulation defects.

These studies confirm 2 key findings: first, that 43%-63% of tests are potentially inaccurate or of low utility, and second, that inpatient thrombophilia testing can be costly. Importantly, the costs of inappropriate testing were likely underestimated. For example, Mou et al. excluded 16.6% of tests that were performed for reasons that could not always be easily justified—such as "tests ordered with no documentation or justification" or "work-up sent solely on suspicion of possible thrombotic event without diagnostic confirmation." Additionally, Mou et al. defined appropriateness more generously than current guidelines; for example, "recurrent provoked VTE" was listed as an appropriate indication for thrombophilia testing, although this is not supported by current guidelines for inherited thrombophilia evaluation. Similarly, Cox et al included cryptogenic stroke as an appropriate indication to perform thrombophilia testing; however, current American Heart Association and American Stroke Association guidelines state that usefulness of screening for hypercoagulable states in such patients is unknown.[7] Furthermore, APS testing is not recommended in all cases of cryptogenic stroke in the absence of other clinical manifestations of APS.[7]

It remains puzzling why physicians continue to order inpatient thrombophilia testing despite their low clinical utility and inaccurate results. Cox and colleagues suggested that a lack of clinician and patient education may explain part of this reason. Likewise, easy access to "thrombophilia panels" make it easy for any clinician to order a number of tests that appear to be expert endorsed due to their inclusion in the panel. Cox et al. found that 79% of all thrombophilia tests were ordered as a part of a panel. Finally, patients and clinicians are continually searching for a reason why the thromboembolic event occurred. The thrombophilia test results (even if potentially inaccurate), may lead to a false sense of relief for both parties, no matter the results. If a thrombophilia is found, then patients and clinicians often have a sense for why the thrombotic event occurred. If the testing is negative, there may be a false sense of reassurance that "no genetic" cause for thrombosis exists.[8]

How can we improve care in this regard? Given the magnitude of financial and psychological cost of inappropriate inpatient thrombophilia testing,[9] a robust deimplementation effort is needed.[10,11] Electronic-medical-record–based solutions may be the most effective tool to educate physicians at the point of care while simultaneously deterring inappropriate ordering. Examples include eliminating tests without evidence of clinical utility in the inpatient setting (ie, methylenetetrahydrofolate reductase); using hard stops to prevent unintentional duplicative tests[12]; and preventing providers from ordering tests that are not reliable in certain settings—such as protein S activity when patients are receiving warfarin. The latter intervention would have pre-

***Address for correspondence and reprint requests:** Lauren Heidemann, MD, 1500 E Medical Center Drive, SPC 5376, Ann Arbor, MI, 48109-5376; Telephone: 734-647-6928; Fax: 734-232-9343; E-mail: lheidema@med.umich.edu

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vented 16% of tests (on 44% of the patients) performed in the Cox et al study. Other promising efforts include embedding guidelines into order sets and requiring the provider to choose a guideline-based reason before being allowed to order such a test. Finally, eliminating thrombophilia "panels" may reduce unnecessary duplicate testing and avoid giving a false sense of clinical validation to ordering providers who may not be familiar with the indications or nuances of each individual test.

In light of mounting evidence, including the 2 important studies discussed above, it is no longer appropriate or wise to allow unfettered access to thrombophilia testing in hospitalized patients. The evidence suggests that these tests are often ordered without regard to expense, utility, or accuracy in hospital-based settings. Deimplementation efforts that provide hard stops, education, and limited access to such testing in the electronic medical ordering system when ordering thrombophilia workups now appear necessary.

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Does the Week-End Justify the Means?

Kieran L. Quinn, MD, MSc,[1] Chaim M. Bell, MD, PhD[2*]

[1]Department of Medicine, University of Toronto, Toronto, Ontario, Canada; [2]Department of Medicine, Sinai Health System, Toronto, Ontario, Canada.

Let's face it—rates of hospital admission are on the rise, but there are still just 7 days in a week. That means that patients are increasingly admitted on weekdays and on the weekend, requiring more nurses and doctors to look after them. Why then are there no lines for coffee on a Saturday? Does this reduced intensity of staffing translate into worse care for our patients?

Since one of its earliest descriptions in hospitalized patients, the "weekend effect" has been extensively studied in various patient populations and hospital settings.[1-5] The results have been varied, depending on the place of care,[6] reason for care, type of admission,[5,7] or admitting diagnosis.[1,8,9] Many researchers have posited the drivers behind the weekend effect, including understaffed wards, intensity of specialist care, delays in procedural treatments, or severity of illness, but the truth is that we still don't know.

Pauls et al. performed a robust systematic review and meta-analysis examining the rates of in-hospital mortality in patients admitted on the weekend compared with those admitted on weekdays.[10] They analyzed predetermined subgroups to identify system- and patient-level factors associated with a difference in weekend mortality.

A total of 97 studies—comprising an astounding 51 million patients—was included in the study. They found that individuals admitted on the weekend carried an almost 20% increase in the risk of death compared with those who landed in hospital on a weekday. The effect was present for both in-hospital deaths and when looking specifically at 30-day mortality. Translating these findings into practice, an additional 14 deaths per 1000 admissions occur when patients are admitted on the weekend. Brain surgery can be less risky.[11]

Despite this concerning finding, no individual factor was identified that could account for the effect. There was a 16% and 11% increase in mortality in weekend patients associated with decreased hospital staffing and delays to procedural therapies, respectively. No differences were found when examining reduced rates of procedures or illness severity on weekends compared with weekdays. But one must always interpret subgroup analyses, even prespecified ones, with caution because they often lack the statistical power to make concrete conclusions.

To this end, an important finding of the study by Pauls et al. highlights the variation in mortality risk as it relates to the weekend effect.[10] Even for individuals with cancer, a disease with a relatively predictable rate of decline, there are weekend differences in mortality risk that depend upon the type of cancer.[8,12] This heterogeneity persists when examining for the possible factors that contribute to the effect, introducing a significant amount of noise into the analysis, and may explain why research to date has been unable to find the proverbial black cat in the coal cellar.

One thing Pauls et al. makes clear is that the weekend effect appears to be a real phenomenon, despite significant heterogeneity in the literature.[10] Only a high-quality, systematic review has the capability to draw such conclusions. Prior work demonstrates that this effect is substantial in some individuals, and this study confirms that it perseveres beyond an immediate time period following admission.[1,9] The elements contributing to the weekend effect remain undefined and are likely as complex as our healthcare system itself.

Society and policy makers should resist the tantalizing urge to invoke interventions aimed at fixing this issue before fully understanding the drivers of a system problem. The government of the United Kingdom has decreed a manifesto to create a "7-day National Health Service," in which weekend services and physician staffing will match that of the weekdays. Considering recent labor tensions between junior doctors in the United Kingdom over pay and working hours, the stakes are at an all-time high.

But such drastic measures violate a primary directive of quality improvement science to study and understand the problem before reflexively jumping to solutions. This will require new research endeavors aimed at determining the underlying factor(s) responsible for the weekend effect. Once we are confident in its cause, only then can careful evaluation of targeted interventions aimed at the highest-risk admissions be instituted. As global hospital and healthcare budgets bend under increasing strain, a critical component of any proposed intervention must be to examine the cost-effectiveness in doing so. Because the weekend effect is one of increased mortality, it will be hard to justify an acceptable price for an individual's life. And it is not as straightforward as a randomized trial examining the efficacy of parachutes. Any formal evaluation must account for the unintended consequences and opportunity costs of implementing a potential fix aimed at minimizing the weekend effect.

The weekend effect has now been studied for over 15 years. Pauls et al. add to our knowledge of this phenomenon, confirming that the overall risk of mortality for patients admitted on the weekend is real, variable, and substantial.[10] As

***Address for correspondence and reprint requests:** Chaim M. Bell, MD, PhD, Sinai Health System, Department of Medicine, 600 University Ave. Room 427, Toronto, ON, Canada M5G 1X5. ; Telephone: 416-586-4800 x2583 ; Fax: 416-586-8350; E-mail: CBell@mtsinai.on.ca

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more individuals are admitted to hospitals, resulting in increasing numbers of admissions on the weekend, a desperate search for the underlying cause must be carried out before we can fix it. Whatever the means to the end, our elation will continue to be tempered by a feeling of uneasiness every time our coworkers joyously exclaim, "TGIF!"

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Reducing Routine Labs—Teaching Residents Restraint

Michael I. Ellenbogen, MD[1]*, Kevin J. O'Leary, MD, MS[2]

[1]Hospitalist Program, Division of General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; [2]Division of Hospital Medicine, Feinberg School of Medicine, Northwestern University, Chicago, Illinois.

Inappropriate resource utilization is a pervasive problem in healthcare, and it has received increasing emphasis over the last few years as financial strain on the healthcare system has grown. This waste has led to new models of care—bundled care payments, accountable care organizations, and merit-based payment systems. Professional organizations have also emphasized the provision of high-value care and avoiding unnecessary diagnostic testing and treatment. In April 2012, the American Board of Internal Medicine (ABIM) launched the *Choosing Wisely* initiative to assist professional societies in putting forth recommendations on clinical circumstances in which particular tests and procedures should be avoided.

Until recently, teaching cost-effective care was not widely considered an important part of internal medicine residency programs. In a 2010 study surveying residents about resource utilization feedback, only 37% of internal medicine residents reported receiving any feedback on resource utilization and 20% reported receiving regular feedback.[1] These findings are especially significant in the broader context of national healthcare spending, as there is evidence that physicians who train in high-spending localities tend to have high-spending patterns later in their careers.[2] Another study showed similar findings when looking at region of training relative to success at recognizing high-value care on ABIM test questions.[3] The Accreditation Council for Graduate Medical Education has developed the Clinical Learning Environment Review program to help address this need. This program provides feedback to teaching hospitals about their success at teaching residents and fellows to provide high-value medical care.

Given the current zeitgeist of emphasizing cost-effective, high-value care, appropriate utilization of routine labs is one area that stands out as an especially low-hanging fruit. The Society of Hospital Medicine, as part of the *Choosing Wisely* campaign, recommended minimizing routine lab draws in hospitalized patients with clinical and laboratory stability.[4] Certainly, avoiding unnecessary routine lab draws is ideal because it saves patients the pain of superfluous phlebotomy, allows phlebotomy resources to be directed to blood draws with actual clinical utility, and saves money. There is also good evidence that hospital-acquired anemia, an effect of overuse of routine blood draws, has an adverse impact on morbidity and mortality in postmyocardial infarction patients[5,6] and more generally in hospitalized patients.[7]

Several studies have examined lab utilization on teaching services. Not surprisingly, the vast majority of test utilization is attributable to the interns (45%) and residents (26%), rather than attendings.[8] Another study showed that internal medicine residents at one center had a much stronger self-reported predilection for ordering daily recurring routine labs rather than one-time labs for the following morning when admitting patients and when picking up patients, as compared with hospitalist attendings.[9] This self-reported tendency translated into ordering more complete blood counts and basic chemistry panels per patient per day. A qualitative study looking at why internal medicine and general surgery residents ordered unnecessary labs yielded a number of responses, including ingrained habit, lack of price transparency, clinical uncertainty, belief that the attending expected it, and absence of a culture emphasizing resource utilization.[10]

In this issue of the *Journal of Hospital Medicine*, Kurtzman and colleagues report on a mixed-methods study looking at internal medicine resident engagement at their center with an electronic medical record–associated dashboard providing feedback on lab utilization.[11] Over a 6-month period, the residents randomized into the dashboard group received weekly e-mails while on service with a brief synopsis of their lab utilization relative to their peers and also a link to a dashboard with a time-series display of their relative lab ordering. While the majority of residents (74%) opened the e-mail, only a minority (21%) actually accessed the dashboard. Also, there was not a statistically significant relationship between dashboard use and lab ordering, though there was a trend to decreased lab ordering associated with opening the dashboard. The residents who participated in a focus group expressed both positive and negative opinions on the dashboard.

This is one example of social comparison feedback, which aims to improve performance by providing information to physicians on their performance relative to their peers. It has been shown to be effective in other areas of clinical medicine like limiting antibiotic overutilization in patients with upper respiratory infections.[12] One study examining social comparison feedback and objective feedback found that social comparison feedback improved performance for a simulated work task more for high performers but less for low performers than standard objective feedback.[13] The utility of this type of feedback has not been extensively studied in healthcare.

***Address for correspondence and reprint requests:** Michael I. Ellenbogen, MD, Hospitalist Program, Division of General Internal Medicine, Johns Hopkins School of Medicine, Baltimore, Maryland; Telephone: 443-287-4362; Fax: 410-502-0923; E-mail: mellenb6@jhmi.edu

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However, the audit and feedback strategy, of which social comparison feedback is a subtype, has been extensively studied in healthcare. A 2012 Cochrane Review found that audit and feedback leads to "small but potentially important improvements in professional practice."[14] They found a wide variation in the effect of feedback among the 140 studies they analyzed. The factors strongly associated with a significant improvement after feedback were as follows: poor performance at baseline, a colleague or supervisor as the one providing the audit and feedback, repetitive feedback, feedback given both verbally and in writing, and clear advice or guidance on how to improve. Many of these components were missing from this study—that may be one reason the authors did not find a significant relationship between dashboard use and lab ordering.

A number of interventions, however, have been shown to decrease lab utilization, including unbundling of the components of the metabolic panel and disallowing daily recurring lab orders,[15] fee displays,[16] cost reminders,[17] didactics and data feedback,[18] and a multifaceted approach (didactics, monthly feedback, checklist, and financial incentives).[19] A multipronged strategy, including an element of education, audit and feedback, hard-stop limits on redundant lab ordering, and fee information is likely to be the most successful strategy to reducing lab overutilization for both residents and attending physicians. Resource overutilization is a multifactorial problem, and multifactorial problems call for multifaceted solutions. Moreover, it may be necessary to employ both "carrot" and "stick" elements to such an approach, rewarding physicians who practice appropriate stewardship, but also penalizing practitioners who do not appropriately adjust their lab ordering tendencies after receiving feedback showing overuse.

Physician behavior is difficult to change, and there are many reasons why physicians order inappropriate tests and studies, including provider uncertainty, fear of malpractice litigation, and inadequate time to consider the utility of a test. Audit and feedback should be integrated into residency curriculums focusing on high-value care, in which hospitalists should play a central role. If supervising attendings are not integrated into such curriculums and continue to both overorder tests themselves and allow residents to do so, then the informal curriculum will trump the formal one.

Physicians respond to incentives, and appropriately designed incentives should be developed to help steer them to order only those tests and studies that are medically indicated. Such incentives must be provided alongside audit and feedback with appropriate goals that account for patient complexity. Ultimately, routine lab ordering is just one area of overutilization in hospital medicine, and the techniques that are successful at reducing overuse in this arena will need to be applied to other aspects of medicine like imaging and medication prescribing.

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In Reference to: "Cost and Utility of Thrombophilia Testing"

Julie A. Lynch, PhD, RN, MBA[1], Brygida Berse, PhD[2], M. Scott Bowen, MPH[3], Scott D. Grosse, PhD[4]

[1]Department of Veterans Affairs, Salt Lake City Health Care System, Salt Lake City, Utah; [2]School of Medicine, Boston University, Boston, Massachusetts; [3]Office of Public Health Genomics, Centers for Disease Control and Prevention, Atlanta, Georgia; [4]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia.

The article by Petrilli et al. points to the important but complicated issue of ordering laboratory testing for thrombophilia despite multiple guidelines that dispute the clinical utility of such testing for many indications.[1] We question the basis of these authors' assertion that Medicare spends $300 to $672 million for thrombophilia testing annually. They arrived at this figure by multiplying the price of a thrombophilia test panel (between $1100 and $2400) by the number of annual Medicare claims for thrombophilia analysis, which they estimated at 280,000. The price of the panel is derived from two papers: (1) a 2001 review[2] that lists prices of various thrombophilia-related tests adding up to $1782, and (2) a 2006 evaluation by Somma et al.[3] of thrombophilia screening at one hospital in New York in 2005. The latter paper refers to various thrombophilia panels from Quest Diagnostics with list prices ranging from $1311 to $2429. However, the repertoire of available test panels and their prices have changed over the last decade. The cost evaluation of thrombophilia testing should be based on actual current payments for tests, and not on list prices for laboratory offerings from over a decade ago. Several laboratories offer mutational analysis of 3 genes—*F5*, *F2*, and *MTHFR*—as a thrombophilia risk panel. Based on the Current Procedural Terminology (CPT) codes listed by the test suppliers (81240, 81241, and 81291), the average Medicare payment for the combination of these 3 markers in 2013 was $172.[4] A broader panel of several biochemical, immunological, and genetic assays had a maximum Medicare payment in 2015 of $405 (Table).[5]

Also, the annual number of Medicare claims for thrombophilia evaluation was not documented by Petrilli et al.[1] In support of the estimate of 280,000 Medicare claims for thrombophilia testing in 2014, the authors cite Somma et al.,[3] but that paper referred to 275,000 estimated new venous thromboembolism cases in the United States, not the number of claims for thrombophilia testing for all payers, let alone for Medicare. In 2013, Medicare expenditures for genetic testing of the three markers that could be identified by unique CPT codes (*F2*, *F5*, and *MTHFR*) amounted to $33,235,621.[4] This accounts only for DNA analysis, not the functional testing of various components of blood clotting cascade, which may precede or accompany genetic testing.

In conclusion, the cost evaluation of thrombophilia screening is more challenging than the calculation by Petrilli et al. suggests.[1] Even if Medicare paid as much as $400 per individual tested and assuming up to 200,000 individuals underwent thrombophilia testing per year, the aggregate Medicare expenditure would have been no more than roughly $80 million. Thus, the estimated range in the article appears to have overstated actual Medicare expenditures by an order of magnitude. This does not take away from their overall conclusion that payers are burdened with significant expenditures for laboratory testing that may not present clinical value for many patients.[6] We need research into the patterns of utilization as well as improvements in documentation of expenditures associated with these tests.

TABLE. Medicare Prices of Individual Codes Used for Billing for Labcorp Thrombotic Risk Assessment Panel

CPT Code	2015 Medicare Price (National Limit)
81240	$67.03
83090	$22.98
85300	$16.15
85303	$18.84
85306	$20.88
85307	$20.88
85420	$8.90
85613	$13.05
85732	$8.81
86146(x3)	$103.98
86147(x3)	$103.98
Total	$405.48

NOTE: Abbreviation: CPT, Current Procedural Terminology.

Disclosure: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the Department of Veterans Affairs, or the United States government. The authors have nothing to disclose.

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Address for correspondence and reprint requests: Julie A. Lynch, PhD, RN, MBA; Julie.Lynch@va.gov.

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The Authors Reply: "Cost and Utility of Thrombophilia Testing"

Christopher M. Petrilli, MD[1,2*], Lauren Heidemann, MD[1,2], Megan Mack, MD[1,2], Paul Durance, PhD[3], Vineet Chopra, MD, MSc[1,2]

[1]Department of Internal Medicine, Division of Hospital Medicine, University of Michigan, Ann Arbor, Michigan; [2]VA Ann Arbor Healthcare System, Ann Arbor, Michigan; [3]Department of Quality Improvement Operations, Michigan Medicine, University of Michigan, Ann Arbor, Michigan.

We thank Dr. Berse and colleagues for their correspondence about our paper.[1,2] We are pleased they agreed with our conclusion: Thrombophilia testing has limited clinical utility in most inpatient settings.

Berse and colleagues critiqued details of our methodology in calculating payer cost, including how we estimated the number of Medicare claims for thrombophilia testing. We estimated that there were at least 280,000 Medicare claims in 2014 using CodeMap® (Wheaton Partners, LLC, Schaumburg, IL), a dataset of utilization data from the Physician Supplier Procedure Summary Master File from all Medicare Part B carriers.[3] This estimate was similar to that reported in a previous publication.[4]

Berse and colleagues generated a lower cost estimate of $405 for 11 of the 13 thrombophilia tests referenced in our paper (excluding factor V and methylenetetrahydrofolate reductase mutations) by using the average Medicare payment.[2] However, private insurance companies or self-paying patients often pay multiples of Medicare reimbursement. Our institutional data suggest that the average reimbursement across all payors not based on a diagnosis-related group for 12 of these 13 tests is $1,327 (Table). Importantly, these expenses do not factor in costs related to increased premiums for health, disability, and life insurance that may occur due to an inappropriately ordered, positive thrombophilia test. Nor, for that matter, do they include the psychological stress of the patient that may result from a positive genetic test.

Thus, regardless of the precise estimates, even a conservative estimate of 33 to 80 million dollars of unnecessary spending is far too much. Rather, it is a perfect example of "Things We Do for No Reason."

TABLE. Charges and Reimbursement at Michigan Medicine for Thrombophilia Tests

CPT Code	Test Name	Charge ($)	Reimbursement ($)
81240	F2 (Prothrombin, Coagulation Factor II) Gene Analysis	654	218
81241	Factor V (Leiden) Mutation (R506q)	654	218
81291	MTHFR (Methylenetetrahydrofolate Reductase)	675	225
83090	Homocysteine	114	38
85300	Antithrombin III Activity	503	168
85303	Protein C, Activity	197	66
85306	Protein S Antigen	226	75
85307	Activated Protein C Resistance	156	52
85420	Plasminogen Activity	422	141
85613	DRVVT Screen, DRVVT Confirm, and DRVVT 1:1 Mix	173	58
85732	Lupus Anticoagulant and Antiphospholipid Antibody Confirmatory Profile	Data not available	Data not available
86146(x3)	Beta-2-Glycoprotein I Antibodies (IgG, IgA, IgM)	36	12
86147(x3)	Cardiolipin Antibody	170	57

[a]Average reimbursement across non-Diagnosis-Related Group (DRG)-based payors.

NOTE: Abbreviations: CPT, current procedural terminology; DRVVT, Dilute Russell's viper venom time; Ig, immunoglobulin.

Disclosure: Nothing to report.

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***Address for correspondence and reprint requests:** Christopher Petrilli, MD, Michigan Medicine,1500 E. Medical Center Drive, Ann Arbor, MI 48105. Telephone: 734-936-5582; Fax: 734-647-9443; E-mail: cpetrill@med.umich.edu

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What Can Be Done to Maintain Positive Patient Experience and Improve Residents' Satisfaction? In Reference to: "Standardized Attending Rounds to Improve the Patient Experience: A Pragmatic Cluster Randomized Controlled Trial"

Goutham Talari, MD*, Aibek E Mirrakhimov, MD, Preetham Talari, MD, Romil Chadha, MD, MPH, Saurabh Parasramka, MD

Division of Hospital Medicine, Department of Internal Medicine, University of Kentucky, Lexington, Kentucky.

We read the article by Monash et al.[1] published in the March 2017 issue with great interest. This randomized study showed a discrepancy between patients' and residents' satisfaction with standardized rounds; for example, residents reported less autonomy, efficiency, teaching, and longer time of rounds.

We agree that letting residents lead the rounds with minimal participation of an attending (only when needed) may improve resident satisfaction. Other factors, such as quality of teaching, positive comments to learners during bedside rounds (whenever appropriate), and a positive attending attitude, might be helpful.[2,3] We believe that the adaptation of such a model through the prism of residents' benefit will lead to better satisfaction among trainees.

On the other hand, we note that the nature of the study might have exaggerated patient satisfaction when compared with real-world surveys.[4] The survey appears to focus only on attending rounds and did not consider other factors like hospitality, pain control, etc. A low patient census and lack of double blinding are other potential factors.

In conclusion, we want to congratulate the authors for raising this important topic and showing positive patients' satisfaction with standardized rounds on teaching services. Further research should focus on improving residents' satisfaction without compromising patients' experiences.

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***Address for correspondence and reprint requests:** Goutham Talari, MD, University of Kentucky Hospital, A. B. Chandler Medical Center, 800 Rose Street, MN 602, Lexington, KY, 40536; Telephone: 859-323-6047; Fax: 859-257-3873; E-mail: goutham.talari@uky.edu

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The Authors Reply, "What Can Be Done to Maintain Positive Patient Experience and Improve Residents' Satisfaction?" and "Standardized Attending Rounds to Improve the Patient Experience: A Pragmatic Cluster Randomized Controlled Trial"

Bradley Monash, MD, Margaret C. Fang, MD, MPH, James Harrison, PhD

Division of Hospital Medicine, The University of California, San Francisco, California.

We thank Talrai et al. for their comments in response to our randomized controlled trial evaluating the impact of standardized rounds on patient, attending, and trainee satisfaction. We agree that many factors beyond rounding structure contribute to resident satisfaction, including those highlighted by the authors, and would enthusiastically welcome additional research in this realm.

Because our study intervention addressed rounding structure, we elected to specifically focus on satisfaction with rounds, both from the physician and patient perspectives. We chose to ask about patient satisfaction with attending rounds, as opposed to more generic measures of patient satisfaction, to allow for more direct comparison between attending/resident responses and patient responses. Certainly, there are many other factors that affect overall patient experience. Surveys such as Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) and Press Ganey do not specifically address rounds, are often completed several weeks following hospitalization, and may have low response rates. Relying on such global assessments of patient experience may also reduce the power of the study. Although patient responses to our survey may be higher than scores seen with HCAHPS and Press Ganey, the randomized nature of our study helps control for other differences in the hospitalization experience unrelated to rounding structure. Similarly, because physician teams were randomly assigned, differences in census were not a major factor in the study. Physician blinding was not possible due to the nature of the intervention, which may have affected the satisfaction reports from attendings and residents. For our primary outcome (patient satisfaction with rounds), patients were blinded to the nature of our intervention, and all study team members involved in data collection and statistical analyses were blinded to study arm allocation.

In summary, we feel that evaluating the trade-offs and consequences of interventions should be examined from multiple perspectives, and we welcome additional investigations in this area.

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