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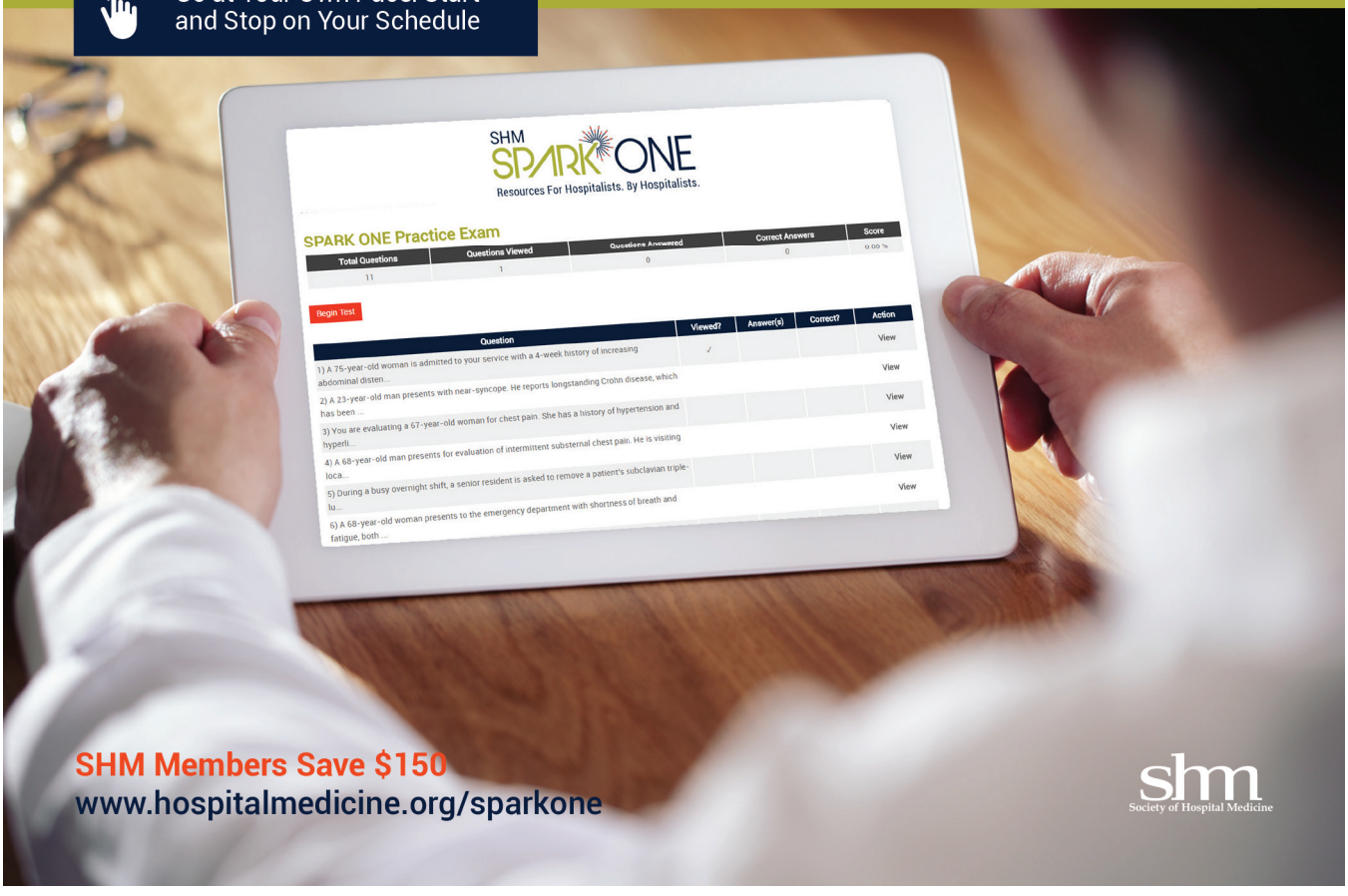

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Publisher: The Journal of Hospital Medicine (Print ISSN 1553-5592; E-ISSN 1553-5606) is published monthly for the Society of Hospital Medicine by Frontline Medical Communications, with business offices at 7 Century Drive, Suite 302, Parsippany, NJ 07054-4609, telephone 973-206-3434, fax 973-206-9378. Periodicals postage paid at Parsippany, NJ and at additional mailing offices.

Postmaster: Send address changes to Journal of Hospital Medicine, Subscription Service, 151 Fairchild Ave, Suite 2, Plainview, NY 11803-1709.

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EDITORIALS

Association of Inpatient Antimicrobial Utilization Measures with Antimicrobial Stewardship Activities and Facility Characteristics of Veterans Affairs Medical Centers

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BACKGROUND: Antimicrobial stewardship programs (ASPs) have been advocated to improve antimicrobial utilization, but program implementation is variable.

OBJECTIVE: To determine associations between ASPs and facility characteristics, and inpatient antimicrobial utilization measures in the Veterans Affairs (VA) system in 2012.

DESIGN: In 2012, VA administered a survey on antimicrobial stewardship practices to designated ASP contacts at VA acute care hospitals. From the survey, we identified 34 variables across 3 domains (evidence, organizational context, and facilitation) that were assessed using multivariable least absolute shrinkage and selection operator regression against 4 antimicrobial utilization measures from 2012: aggregate acute care antimicrobial use, antimicrobial use in patients with non-infectious primary discharge diagnoses, missed opportunities to convert from parenteral to oral antimicrobial therapy, and double anaerobic coverage.

SETTING: All 130 VA facilities with acute care services.

RESULTS: Variables associated with at least 3 favorable changes in antimicrobial utilization included presence of postgraduate physician/pharmacy training programs, number of antimicrobial-specific order sets, frequency of systematic de-escalation review, presence of pharmacists and/or infectious diseases (ID) attendings on acute care ward teams, and formal ID training of the lead ASP pharmacist. Variables associated with 2 unfavorable measures included bed size, the level of engagement with VA Antimicrobial Stewardship Task Force online resources, and utilization of antimicrobial stop orders.

CONCLUSIONS: Formalization of ASP processes and presence of pharmacy and ID expertise are associated with favorable utilization. Systematic de-escalation review and order set establishment may be high-yield interventions. *Journal of Hospital Medicine* 2017;12:301-309. © 2017 Society of Hospital Medicine

The deleterious impact of inappropriate and/or excessive antimicrobial usage is well recognized. In the United States, the Centers for Disease Control and Prevention (CDC) estimates that at least 2 million people become infected with antimicrobial-resistant bacteria with 23,000 subsequent deaths and at least $1 billion in excess medical costs per year.[1]

In response, many healthcare organizations have developed antimicrobial stewardship programs (ASPs). Guidelines co-sponsored by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America, as well as recent statements from the CDC and the Transatlantic Taskforce on Antimicrobial Resistance, all recommend core ASP elements.[2-5] The guidelines provide general recommendations on ASP structure, strategies, and activities. The recommended ASP structure is a team of physicians and pharmacists that collaborates with facility governing committees and other stakeholders to optimize antimicrobial use. While personnel with expertise in infectious diseases (ID) often lead ASPs, hospitalists are also recognized as key contributors, especially in quality improvement.[6,7] Recommended strategies include prospective audit of antimicrobial use with intervention and feedback and formulary restriction with preauthorization. Recommended activities include education, creation of guidelines, clinical pathways, and order forms, and programs to promote de-escalation and conversion from parenteral (IV) to oral (PO) antimicrobial therapy. However, limited evidence exists regarding the effectiveness of these ASP core elements.[8,9] While Cochrane reviews found clear evidence that particular stewardship strategies (eg, audit and feedback, formulary restriction, guidelines implemented with or without feedback, protocols, computerized decision support) can be effective in reducing antimicrobial usage and improving clinical outcomes over the long term, little evidence exists favoring 1 strategy over

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Additional Supporting Information may be found in the online version of this article.

Received: July 25, 2016; **Revised**: October 3, 2016; **Accepted**: October 18, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2730

another.[8] Furthermore, most individual studies of ASPs are single-center, making their conclusions less generalizable.

In 2012, the VA National Antimicrobial Stewardship Task Force (ASTF), in conjunction with the VA Healthcare Analysis and Information Group (HAIG) administered a survey on the characteristics of ASPs at all 130 acute care VA facilities (Appendix A). We used these survey results to build an implementation model and then assess associations between facility-level variables and 4 antimicrobial utilization measures.

METHODS

Survey and Data

In 2011, the ASTF was chartered to develop, deploy, and monitor a strategic plan for optimizing antimicrobial therapy management. Monthly educational webinars and sample policies were offered to all facilities, including a sample business plan for stewardship and policies to encourage de-escalation from broad-spectrum antimicrobials, promote conversion from parenteral to oral antimicrobial therapy, avoid unnecessary double anaerobic coverage, and mitigate unnecessary antimicrobial usage in the context of *Clostridium difficile* infection.[10]

At the time that ASTF was chartered, the understanding of how ASP structures across VA facilities operated was limited. Hence, to capture baseline institutional characteristics and stewardship activities, ASTF and HAIG developed an inventory assessment of ASPs that was distributed online in November 2012. All 130 VA facilities providing inpatient acute care services responded.

We derived 57 facility characteristics relevant to antimicrobial utilization and conducted a series of factor analyses to simplify the complex dataset, and identify underlying latent constructs. We categorized resulting factors into domains of evidence, context, or facilitation as guided by the Promoting Action on Research Implementation in Health Services framework.[11] Briefly, the evidence domain describes how the facility uses codified and noncodified sources of knowledge (eg, research evidence, clinical experience). Organizational context comprises a facility's characteristics that ensure a more conducive environment to put evidence into practice (eg, supportive leadership, organizational structure, evaluative systems). Facilitation emphasizes a facility personnel's "state of preparedness" and receptivity to implementation.

Using factor analysis to identify facility factors as correlates of the outcomes, we first examined polychoric correlations among facility characteristics to assess multicollinearity. We performed independent component analysis to create latent constructs of variables that were defined by factor loadings (that indicated the proportion of variance accounted for by the construct) and uniqueness factors (that determined how well the variables were interpreted by the construct). Factors retained included variables that had uniqueness values of less than 0.7 and factor loadings greater than 0.3. Those associated with uniqueness values greater than 0.7 were left as single items, as were characteristics deemed a priori to be particularly important to antimicrobial stewardship. Factor scales that had only 2 items were converted into indices, while factor scores were generated for those factors that contained 3 or more items.[12-15]

Data for facility-level antimicrobial utilization measures were obtained from the VA Corporate Data Warehouse from calendar year 2012. The analysis was conducted within the VA Informatics and Computing Infrastructure. All study procedures were approved by the VA Central Institutional Review Board.

Measures

Four utilization measures were defined as dependent measures: overall antimicrobial use; antimicrobial use in patients with non-infectious discharge diagnoses; missed opportunities to convert from parenteral to oral antimicrobial therapy; and missed opportunities to avoid double anaerobic coverage with metronidazole.

Overall antimicrobial use was defined as total acute care (ie, medical/surgical/intensive care) antibacterial use for each facility aggregated as per CDC National Healthcare Safety Network Antimicrobial Use Option guidelines (antimicrobial days per 1000 patient days present). A subanalysis of overall antimicrobial use was restricted to **antimicrobial use among patients without an infection-related discharge diagnosis**, as we surmised that this measure may capture a greater proportion of potentially unnecessary antimicrobial use. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)[16] codes for infectious processes were identified by a combination of those classified previously in the literature,[17] and those identified by finding the descendants of all infections named in the Systematized Nomenclature of Medicine--Clinical Terms.[18] Next, all remaining codes for principal discharge diagnoses for which antimicrobials were administered were reviewed for potential indications for systemic antibacterial use. Discharges were considered noninfectious if no codes were identified when systemic antimicrobials were or could be indicated. For this measure, antimicrobial days were not counted if administered on or 1 day after the calendar day of surgery warranting antimicrobial prophylaxis.

Missed opportunities for conversion from parenteral to oral (IV to PO) formulations of highly bioavailable oral antimicrobials (ciprofloxacin, levofloxacin, moxifloxacin, azithromycin, clindamycin, linezolid, metronidazole, and fluconazole) were defined as the percentage of days of unnecessary IV therapy that were given when PO therapy could have been used among patients who were not in intensive care units at the time of antimicrobial administration who were receiving other oral medications, using previously described methodology.[19] **Missed opportunities for avoiding redundant anaerobic coverage with metronidazole** were defined as the percentage of days in which patients receiving metronidazole also received antibiotics with activity against anaerobic bacteria, specifically beta-lactam/beta-lactamase inhibitors, carbapenems, cefotetan/cefoxitin, clindamycin, moxifloxacin, or tige-

cycline), using previously described methodology.[20] Patients for whom *C. difficile* testing was either ordered or positive within the prior 28 days (indicating potential clinical concern for *C. difficile* infection) were excluded from this endpoint.

Analysis

The variables derived above were entered into a multivariable model for each of the 4 antimicrobial utilization measures. The least absolute shrinkage and selection operator (LASSO) regression was used to determine significant associations between variables and individual utilization measures.[21] LASSO was chosen because it offers advantages over traditional subset selection approaches in large multivariable analyses by assessing covariates simultaneously rather than sequentially, supporting prediction rather than estimation of effect.[22] *P* values were not reported as they are not useful in determining statistical significance in this methodology. A tuning parameter of 0.025 was determined for the model based on a cross-validation approach. Significant variables remaining in the model were reported with the percent change in each utilization measure per unit change in the variable of interest. For binary factors, percent change was reported according to whether the variable was present or not. For ordinal variables, percent change was reported according to incremental increase in ordinal score. For continuous variables or variables represented by factor or index scores, percent change was reported per each 25% increase in the range of the score.

RESULTS

Inpatient Facility Antimicrobial Stewardship Characteristics and Antimicrobial Utilization

Frequencies of key facility characteristics that contributed to variable development are included in Table 1. Full survey results across all facilities are included in Appendix B. Factor analysis reduced the total number of variables to 32; however, we also included hospital size and VA complexity score. Thus, 34 variables were evaluated for association with antimicrobial utilization measures: 4 in the evidence domain, 23 in the context domain, and 7 in the facilitation domain (Table 2).

Median facility antimicrobial use was 619 antimicrobial days per 1000 days present (interquartile range [IQR], 554-700; overall range, 346-974). Median facility noninfectious antimicrobial use was 236 per 1000 days present (IQR, 200-286). Missed opportunities for conversion from IV to PO antimicrobial therapy were common, with a median facility value of 40.4% (391/969) of potentially eligible days of therapy (IQR, 32.2-47.8%). Missed opportunities to avoid double anaerobic coverage were less common (median 15.3% (186/1214) of potentially eligible days of therapy (IQR, 11.8%-20.2%; Figure).

Overall Antimicrobial Use

Four variables were associated with decreased overall antimicrobial use, although with small magnitude of change: presence of postgraduate physician/pharmacy training programs (0.03% decrease per quarter increase in factor score; on the order of 0.2 antimicrobial days per 1000 patient days present), presence of pharmacists and/or ID attendings on general medicine ward teams (0.02% decrease per quarter increase in index score), frequency of systematic de-escalation review (0.01% decrease per ordinal increase in score), and degree of involvement of ID physicians and/or fellows in antimicrobial approvals (0.007% decrease per quarter increase in index score). No variables were associated with increased overall antimicrobial use.

Antimicrobial Use among Discharges without Infectious Diagnoses

Six variables were associated with decreased antimicrobial use in patients without infectious discharge diagnoses, while 4 variables were associated with increased use. Variables associated with the greatest magnitude of decreased use included facility educational programs for prudent antimicrobial use (1.8% on the order of 4 antimicrobial days per 1000 patient days present), frequency of systematic de-escalation review (1.5% per incremental increase in score), and whether a facility's lead antimicrobial stewardship pharmacist had ID training (1.3%). Also significantly associated with decreased use was a factor summarizing the presence of 4 condition-specific stewardship processes (de-escalation policies, policies for addressing antimicrobial use in the context of *C. difficile* infection, blood culture review, and automatic ID consults for certain conditions) (0.6% per quarter increase in factor score range), the extent to which postgraduate physician/pharmacy training programs were present (0.6% per quarter increase in factor score range), and the number of electronic antimicrobial-specific order sets present (0.4% per order set). The variables associated with increased use of antimicrobials included the presence of antimicrobial stop orders (4.6%), the degree to which non-ID physicians were involved in antimicrobial approvals (0.7% per increase in ordinal score), the level engagement with ASTF online resources (0.6% per quarter increase in factor score range), and hospital size (0.6% per 50-bed increase).

Missed Opportunities for Parenteral to Oral Antimicrobial Conversion

Missed opportunities for IV to PO antimicrobial conversion had the largest number of significant associations with organizational variables: 14 variables were associated with fewer missed opportunities, while 5 were associated with greater missed opportunities. Variables associated with the largest reductions in missed opportunities for IV to PO conversion included having guidelines for antimicrobial duration (12.8%), participating in regional stewardship collaboratives (8.1%), number of antimicrobial-specific order sets (6.0% per order set), ID training of the ASP pharmacist (4.9%), and VA facility complexity designation (4.2% per quarter increase in score indicating greater complexity).[23] Variables associated with more missed opportunities included stop orders (11.7%), overall perceived receptiveness to antimicro-

TABLE 1. Frequencies of Key Facility Antimicrobial Stewardship Characteristics at VA Facilities Contributing to Variable Development (N=130)

Facility Characteristics	Facilities (n)	(%)
Contributors to evidence domain	103	79
Internal inpatient ID consultation available	120	92
Any restriction of antimicrobial use	47	36
Guidelines for antimicrobial duration (any)	96	74
Written clinical pathways/guidelines for specific conditions (any)		
Contributors to context domain		
At least one full-time attending ID physician at facility	78	60
Dedicated clinical pharmacist in ED	20	18
Presence of outpatient parenteral antimicrobial therapy program	85	65
Facility rates helpfulness of VA ASTF SharePoint site as "very helpful" or "helpful"	82	63
Facility rates helpfulness of ASTF sample policy for intravenous to oral antibiotic conversion as "very helpful" or "helpful"	68	52
Facility rates helpfulness of ASTF sample policy for avoidance of double anaerobic coverage as "very helpful" or "helpful"	51	39
Facility rates helpfulness of ASTF sample policy for improving outcomes in patients with *Clostridium difficile* infection as "very helpful" or "helpful"	51	39
Facility rates helpfulness of ASTF sample business plan as "very helpful" or "helpful"	49	38
Facility identifies more information technology/data tools support as beneficial in achieving optimal antibiotic use	95	73
Facility identifies more support from administration as beneficial in achieving optimal antibiotic use	79	61
Facility identifies more support from pharmacy as beneficial in achieving optimal antibiotic use	75	58
Facility identifies more support from ID physicians as beneficial in achieving optimal antibiotic use	73	56
Facility identifies more prescriber buy-in as beneficial in achieving optimal antibiotic use	77	59
Facility identifies more educational tools support as beneficial in achieving optimal antibiotic use	73	56
Facility identifies more guidelines support as beneficial in achieving optimal antibiotic use	67	52
Surgical residency program	84	65
ID fellowship program	68	52
Pharmacy residency program	102	78
Participation in AS collaborative within geographic region (ie, regional AS conference or committee)	13	10
ID physician approves antibiotics during weekdays	57	44
ID physician approves antibiotics during nights/weekends	39	30
ID pharmacist approves antibiotics during weekdays	44	34
ID pharmacist approves antibiotics during nights/weekends	8	6
Non-ID physician approves antibiotics during weekdays	7	5
Non-ID physician approves antibiotics during nights/weekends	11	8
Formal policy for ASP established	29	22
Policy for de-escalation of antimicrobials	19	15
Policy for intervention on antimicrobial usage in context of *C. difficile* infection	25	19
Timely review of blood cultures to assure appropriate therapy	56	43
Automatic ID consults for certain conditions	36	28
Automatic stop orders for antimicrobial duration	98	75
Electronic antimicrobial order form(s) for any specific antimicrobial	55	42
General medicine service deemed "very receptive" or "receptive" to ASP	110	85
ICU medicine service deemed "very receptive" or "receptive" to ASP	90	69
Facility has AS team	49	38
ID physician is a part of AS team	45	35
Clinical pharmacist/clinical pharmacy specialist is part of AS team	49	38
Antibiograms disseminated via facility intranet	96	74
Antibiograms disseminated via pocket card reference	56	43
Medication use evaluation performed for any antibiotic in prior 2 y	61	47
Provision of group- or provider-specific feedback on patterns of antibiotic use	55	42

Continued on page 305

TABLE 1. Frequencies of Key Facility Antimicrobial Stewardship Characteristics at VA Facilities Contributing to Variable Development (N=130) (continued)

Facility Characteristics	Facilities (n)	(%)
Contributors to context domain		
Reporting of clinical outcomes related to antimicrobial use	71	55
Systematic review for de-escalation performed (always or usually)	39	30
Measurement of antibiotic use in defined daily doses	18	14
Measurement of antibiotic use in days of therapy	19	15
Measurement of antimicrobial expenditures	37	28
Contributors to facilitation domain		
ID physicians attend on medical ward teams	89	68
Clinical pharmacist assigned to acute care teams	118	91
Business plan for ASP approved or in development	41	32
ASP clinical pharmacist/clinical pharmacy specialist with ID training	34	26
Educational programs for prudent antimicrobial use	94	72
Communication to providers on principles of antibiotic use		
E-mail alerts	51	39
Newsletters	37	28
Pharmacy alerts	48	37
Engagement with ASTF outreach efforts:		
Finding ASTF national webinars "very helpful" or "helpful"	70	54
Finding ASTF face-to-face meetings "very helpful" or "helpful"	48	37
Electronic resources used to facilitate ASP activities:		
Basic electronic medical record system	115	88
Proprietary software	14	11
Administrative electronic databases	23	18

NOTE: Abbreviations: AS, antimicrobial stewardship; ASP, antimicrobial stewardship programs; ASTF, antimicrobial stewardship task force; ED, emergency department; ICU, intensive care unit; ID, infectious diseases; VA, Veterans Affairs.

bial stewardship among clinical services (9.4%), the degree of engagement with ASTF online resources (6.9% per quarter increase in factor score range), educational programs for prudent antimicrobial use (4.1%), and hospital size (1.0% per 50-bed increase).

Missed Opportunities for Avoidance of Double Anaerobic Coverage

Four variables were associated with more avoidance of double anaerobic coverage: ID training of the lead ASP pharmacist (8.8%), presence of pharmacists and/or ID attendings on acute care ward teams (6.2% per quarter increase in index score), degree of ID pharmacist involvement in antimicrobial approvals, ranging from not at all (score=0) to both weekdays and nights/weekends (score=2; 4.3% per ordinal increase), and the number of antimicrobial-specific order sets (1.5% per order set). No variables were associated with less avoidance of double anaerobic coverage.

Variables Associated with Multiple Favorable or Unfavorable Antimicrobial Utilization Measures

To better assess the consistency of the relationship between organizational variables and measures of antimicrobial use, we tabulated variables that were associated with at least 3 potentially favorable (ie, reduced overall or noninfectious antimicrobial use or fewer missed opportunities) measures. Altogether, 5 variables satisfied this criterion: the presence of postgraduate physician/pharmacy training programs, the number of antimicrobial-specific order sets, frequency of systematic de-escalation review, the presence of pharmacists and/or ID attendings on acute care ward teams, and formal ID training of the lead ASP pharmacist (Table 3). Three other variables were associated with at least 2 unfavorable measures: hospital size, the degree to which the facility engaged with ASTF online resources, and presence of antimicrobial stop orders.

DISCUSSION

Variability in ASP implementation across VA allowed us to assess the relationship between ASP and facility elements and baseline patterns of antimicrobial utilization. Hospitalists and hospital policy-makers are becoming more and more engaged in inpatient antimicrobial stewardship. While our results suggest that having pharmacists and/or physicians with formal ID training participate in everyday inpatient activities can favorably improve antimicrobial utilization, considerable input into stewardship can be made by hospitalists and policy makers. In particular, based on this work,

TABLE 2. Antimicrobial Stewardship Facility Variables Examined According to PARiHS Domain[a]

No.	Factor Name	Variable Type (range)	Contributing Survey Question(s)/ Data Sources[a]
	Evidence domain		
E1	Availability of inpatient ID consultation (score 0= non-ID physicians or pharmacists handling ID issues; score 5=internal inpatient ID service)	Ordinal (0-5)	Q12
E2	Presence of policies that restrict certain antimicrobials	Binary (0,1)	Q22
E3	Guidelines for antimicrobial duration	Binary (0,1)	Q33
E4	Number of written clinical pathways/guidelines for specific conditions	Ordinal (0-7)	Q25a
	Context domain		
	Structural characteristics		
C1	Facility complexity (level 1a, 1b, 1c, 2, or 3)	Continuous	Internal VA data
C2	Hospital beds (no.)	Ordinal (0-433)	Internal VA data
	Resources		
C3	Full-time ID attendings on site (no.)	Ordinal (0-10)	Q1a
C4	Dedicated clinical pharmacist in ED	Binary (0,1)	Q13
C5	Presence of outpatient parenteral antimicrobial therapy program	Binary (0,1)	Q14
C6	Degree of engagement with VA ASTF (summary of helpfulness ratings of ASTF SharePoint site and sample policies)	Factor score	Q42-46,
C7	Perceived benefit of types of support in achieving optimal antimicrobial use (number of categories of additional support deemed potentially helpful to AS)	Factor score	Q54
	Affiliation/networks		
C8	Presence of postgraduate physician/pharmacy training programs (ID fellowship, surgical residency, pharmacy residency)	Factor score	Q2, Q5, Q7
C9	Participation in stewardship regional collaboratives	Binary (0,1)	Q18
	Decision-making		
C10	Degree of involvement of ID physicians and/or fellows in antimicrobial approvals (ie, during weekdays vs. nights/ weekends)	Index	Q23e,f
C11	Degree of ID pharmacist involvement in antimicrobial approvals	Ordinal (0-2)	Q23e,f
C12	Degree of non-ID physician involvement in antimicrobial approvals	Ordinal (0-4)	Q23e,f
	Formalization		
C13	Presence of formal stewardship policy	Binary	Q17, Q20a
C14	Presence of condition-specific stewardship interventions (number present of de-escalation policies, policies for addressing antimicrobial use in the context of *C difficile* infection, blood culture review, automatic ID consults for certain conditions)	Factor score	Q29, Q31, Q32, Q38
C15	Antimicrobial stop orders in place	Binary (0,1)	Q34
C16	Number of antimicrobial-specific order sets in place	Ordinal (0-9)	Q24
	Receptiveness to change		
C17	Overall receptiveness to stewardship among clinical services (count of clinical services deemed "receptive" or "very receptive")	Factor Score	Q55
	Leadership		
C18	Degree and duration of physician and pharmacy involvement in stewardship (how long ASP has been in place and percentage of time dedicated to ASP by physicians and pharmacists)	Factor Score	Q19, Q19f,g
	Evaluation and feedback		
C19	Degree of dissemination and evaluation of antimicrobial outcome data (number of methods of antibiogram dissemination plus whether MUE has been done on any antibiotic within 2 y)	Index	Q16b, Q52
C20	Degree to which antimicrobial usage and outcomes are reported to providers (frequency of group- or provider-specific feedback on patterns of antimicrobial use and whether reports on clinical outcomes related to antibiotic use are generated)	Index	Q49, Q50a
C21	Frequency of systematic de-escalation review (score 0=never; score 4=always)	Ordinal (0-4)	Q30

Continued on page 307

TABLE 2. Antimicrobial Stewardship Facility Variables Examined According to PARiHS Domain[a] (continued)

No.	Factor Name	Variable Type (range)	Contributing Survey Question(s)/ Data Sources[a]
C22	Measurement of antimicrobial usage in defined daily doses or days of therapy	Binary (0,1)	Q51a,b
C23	Measurement of antimicrobial expenditures	Binary (0,1)	Q51c
	Facilitation domain		
F1	Presence of pharmacists and/or ID attendings on acute care ward teams	Index	Q9a, Q11
F2	Business plan for antimicrobial stewardship (in place or in development)	Ordinal (0-2)	Q47
F3	Lead antimicrobial stewardship pharmacist has ID training	Binary (0,1)	Q19f5d
F4	Educational programs for prudent antimicrobial use	Binary (0,1)	Q35
F5	Number of resources utilized to update providers on antimicrobials (email alerts, newsletters, pharmacy alerts, other)	Ordinal (0-4)	Q36
F6	Level of engagement with ASTF educational resources and/or face-to-face ASTF meetings (combined helpfulness rating of ASTF webinars and meetings)	Index	Q39, Q40
F7	Number of electronic resources used to facilitate AS activities (basic electronic medical record system, proprietary software, administrative databases)	Ordinal (0-2)	Q48

[a]See Appendix A for full set of survey questions and Appendix B for the full survey results.

NOTE: Abbreviations: ASP, antimicrobial stewardship programs; ASTF, antimicrobial stewardship task force; ED, emergency department; ID, infectious diseases; MUE, medication use evaluations; PARiHS, Promoting Action on Research Implementation in Health Services; VA, Veterans Affairs.

the highest yield from an organizational standpoint may be in working to develop order sets within the electronic medical record and systematic efforts to promote de-escalation of broad-spectrum therapy, as well as encouraging hospital administration to devote specific physician and pharmacy salary support to stewardship efforts.

While we noted that finding the ASTF online resources helpful was associated with potentially unfavorable antimicrobial utilization, we speculate that this may represent reverse causality due to facilities recognizing that their antimicrobial usage is suboptimal and thus seeking out sample ASTF policies to implement. The association between the presence of automatic stop orders and potentially unfavorable antimicrobial utilization is less clear since the timeframe was not specified in the survey; it may be that setting stop orders too far in advance may promote an environment in which critical thinking about antimicrobial de-escalation is not encouraged or timely. The larger magnitude of association between ASP characteristics and antimicrobial usage among patients without infectious discharge diagnoses versus overall antimicrobial usage also suggests that clinical situations where infection was of low enough suspicion to not even have the providers eventually list an infectious diagnosis on their discharge summaries may be particularly malleable to ASP interventions, though further exploration is needed in determining how useful this utilization measure may be as a marker for inappropriate antimicrobial use.

Our results complement those of Pakyz et al.[24] who surveyed 44 academic medical facilities in March 2013 to develop an ASP intensity score and correlate this score and

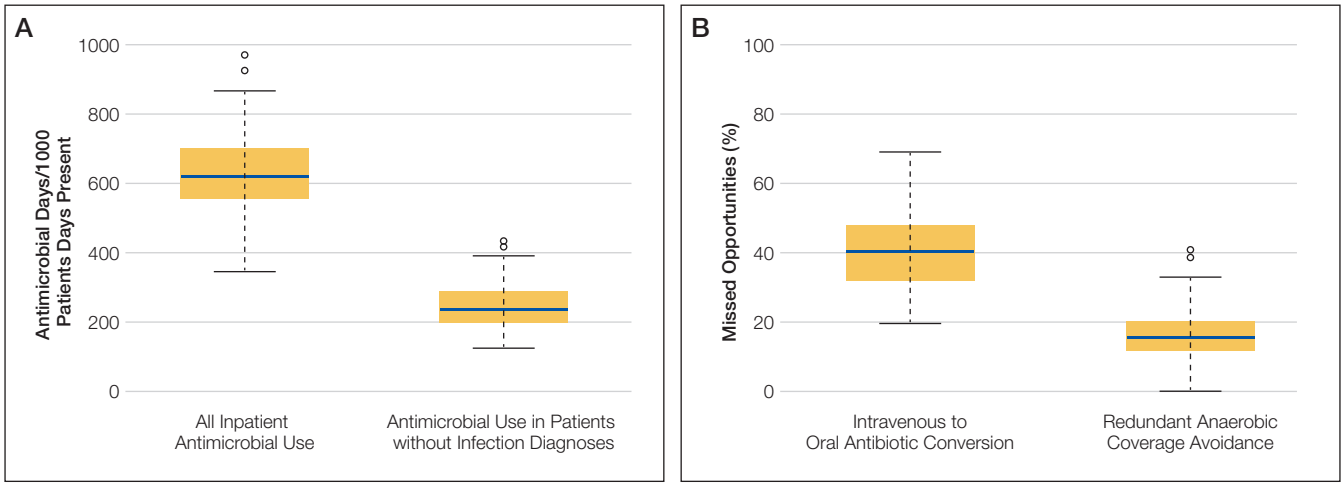

FIG. (A) Overall antimicrobial use and antimicrobial use among patients discharged with no infectious diagnoses. (B) Missed opportunities for parenteral to oral antimicrobial conversion and to avoid potentially unnecessary double anaerobic coverage

NOTE: Box shows median and 25-75 percentiles; whiskers show 5%-95% range; circles represent individual outlier VA facilities.

TABLE 3. Variables Associated with Multiple Antimicrobial Utilization Measures[a,b]

No.	Factor Name	All antimicrobial use	Antimicrobial use in patients with noninfectious primary diagnoses	Parenteral to oral missed opportunities	Avoiding double anaerobic coverage missed opportunities
Associated with multiple potentially favorable utilization					
C8	Presence of postgraduate physician/pharmacy training programs (ID fellowship, surgical residency, pharmacy residency; factor score)	-0.034%	-0.60%	-1.2%	
C16	Number of antimicrobial-specific order sets in place (ordinal, range 0-9)		-0.40%	-6.0%	-1.5%
C21	Frequency of systematic de-escalation review (ordinal, range 0-4)	-0.011%	-1.5%	-0.060%	
F1	Presence of pharmacists and/or ID attendings on acute care ward teams (factor score)	-0.022%		-1.6%	-6.2%
F3	Lead antimicrobial stewardship pharmacist has ID training (binary)		-1.3%	-5.0%	-8.8%
Associated with multiple potentially unfavorable utilization					
C2	Hospital beds (ordinal, range 0-433; percentage change reported for 50-bed increase)		0.62%	1.0%	
C6	Degree to which an individual facility found ASTF sample policies to be helpful (factor score)		0.59%	6.9%	
C15	Antimicrobial stop orders in place (binary)		4.6%	11.7%	

[a]All reported associations with antimicrobial utilization measures are statistically significant using a LASSO (least absolute shrinkage and selection operator)-tuning parameter of 0.025. The magnitude of association is reported as percentage change in the utilization measure according to presence of the factor or not (for binary variables), incremental change in ordinal score (for ordinal factors), and quarter increase in factor score range (for factors for which factor score was reported).

[b]≥3 potentially favorable or ≥2 potentially unfavorable antimicrobial utilization measures.

NOTE: Abbreviations: ASTF, antimicrobial stewardship task force; ID, infectious diseases.

its specific components to overall and targeted antimicrobial use. This study found that the overall ASP intensity score was not significantly associated with total or targeted antimicrobial use. However, ASP strategies were more associated with decreased total and targeted antimicrobial use than were specific ASP resources. In particular, the presence of a preauthorization strategy was associated with decreased targeted antimicrobial use. Our particular findings that order set establishment and de-escalation efforts are associated with multiple antibiotic outcomes also line up with the findings of Schuts et al, who performed a meta-analysis of the effects of meeting antimicrobial stewardship objectives and found that achieving guideline concordance (such as through establishment of order sets) and successfully de-escalating antimicrobial therapy was associated with reduced mortality.[25,26] This meta-analysis, however, was limited by low rigor of its studies and potential for reverse causality. While our study has the advantages of capturing an entire national network of 130 acute care facilities with a 100% response rate, it, too, is limited by a number of issues, most notably by the fact that the survey was not specifically designed for the analysis of antimicrobial utilization measures, patient-level risk stratification was not available, the VA population does not reflect the U.S. population at-large, recall bias, and that antimicrobial prescribing and stewardship practices have evolved in VA since 2012. Furthermore, all of the antimicrobial utilization measures studied are imperfect at capturing inappropriate antibiotic use; in particular, our reliance on principal ICD-9 codes for noninfectious outcomes requires prospective validation. Many survey questions were subjective and subject to misinterpretation; other unmeasured confounders may also be present. Causality cannot be inferred from association. Nevertheless, our findings support many core indicators for hospital ASP recommended by the CDC and the Transatlantic Taskforce on Antimicrobial Resistance,[3,4] most notably, having personnel with ID training involved in stewardship and establishing a formal procedure for ASP review for the appropriateness of an antimicrobial at or after 48 hours from the initial order.

In summary, the VA has made efforts to advance the practice of antimicrobial stewardship system-wide, including a 2014 directive that all VA facilities have an ASP,[27] since the 2012 HAIG assessment reported considerable variability in antimicrobial utilization and antimicrobial stewardship activities. Our study identifies areas of stewardship that may correlate with, positively or negatively, antimicrobial utilization measures that will require further investigation. A repeat and more detailed antimicrobial stewardship survey was recently completed and will help VA gauge ongoing effects of ASTF activities. We hope to re-evaluate our model with newer data when available.

Acknowledgments

The authors wish to thank Michael Fletcher, Jaime Lopez, and Catherine Loc-Carrillo for their administrative and organizational support of the project and Allison Kelly, MD, for her pivotal role in survey development and distribution. This work was supported by the VA Health Services Research and Development Service Collaborative Research to Enhance and Advance Transformation and Excellence (CREATE) Initiative; Cognitive Support Informatics for Antimicrobial Stewardship project (CRE 12-313).

Disclosure: The authors report no financial conflicts of interest.

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High Prevalence of Inappropriate Benzodiazepine and Sedative Hypnotic Prescriptions among Hospitalized Older Adults

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BACKGROUND: Benzodiazepines and sedative hypnotics are commonly used to treat insomnia and agitation in older adults despite significant risk. A clear understanding of the extent of the problem and its contributors is required to implement effective interventions.

OBJECTIVE: To determine the proportion of hospitalized older adults who are inappropriately prescribed benzodiazepines or sedative hypnotics, and to identify patient and prescriber factors associated with increased prescriptions.

DESIGN: Single-center retrospective observational study.

SETTING: Urban academic medical center.

PARTICIPANTS: Medical-surgical inpatients aged 65 or older who were newly prescribed a benzodiazepine or zopiclone.

MEASUREMENTS: Our primary outcome was the proportion of patients who were prescribed a potentially inappropriate benzodiazepine or sedative hypnotic. Potentially inappropriate indications included new prescriptions for insomnia or agitation/anxiety. We used a multivariable random-intercept logistic regression model to identify patient- and prescriber-level variables that were associated with potentially inappropriate prescriptions.

RESULTS: Of 1308 patients, 208 (15.9%) received a potentially inappropriate prescription. The majority of prescriptions, 254 (77.4%), were potentially inappropriate. Of these, most were prescribed for insomnia (222; 87.4%) and during overnight hours (159; 62.3%). Admission to a surgical or specialty service was associated with significantly increased odds of potentially inappropriate prescription compared to the general internal medicine service (odds ratio [OR], 6.61; 95% confidence interval [CI], 2.70-16.17). Prescription by an attending physician or fellow was associated with significantly fewer prescriptions compared to first-year trainees (OR, 0.28; 95% CI, 0.08-0.93). Nighttime prescriptions did not reach significance in initial bivariate analyses but were associated with increased odds of potentially inappropriate prescription in our regression model (OR, 4.48; 95% CI, 2.21-9.06).

CONCLUSIONS: The majority of newly prescribed benzodiazepines and sedative hypnotics were potentially inappropriate and were primarily prescribed as sleep aids. Future interventions should focus on the development of safe sleep protocols and education targeted at first-year trainees. *Journal of Hospital Medicine* 2017;12:310-316. © 2017 Society of Hospital Medicine

Older adults commonly experience insomnia and agitation during hospitalization. Unfortunately, the use of benzodiazepines and sedative hypnotics (BSH) to treat these conditions can be ineffective and expose patients to significant adverse effects.[1,2] Choosing Wisely® is a campaign that promotes dialogue to reduce unnecessary medical tests, procedures, or treatments. This international campaign has highlighted BSHs as potentially harmful and has recommended against their use as first-line treatment of insomnia and agitation.[3-5] Examples of harm with benzodiazepine use include cognitive impairment, impaired postural stability, and an increased incidence of falls and hip fractures in both community and acute care settings.[6-8] In addition, prescriptions initiated in hospital appear to be associated with a higher risk of falls and unplanned readmission.[9,10] The newer nonbenzodiazepine sedative hypnotics, commonly referred to as "z-drugs", were initially marketed as a safer alternative in older adults due to their more favorable pharmacokinetics. Evidence has emerged that they carry similar risks.[6,11,12] A study comparing benzodiazepines and zolpidem found relatively greater risk of fractures requiring hospitalization with the use of zolpidem compared to lorazepam.[13]

The use of benzodiazepines in the acute care setting has been evaluated in a number of studies and ranges from 20% to 45%.[14-16] Few studies focus on the initiation of these medications in BSH-naïve hospitalized patients; however, reports range from 18% to 29%.[17,18] Factors found to be associated with potentially inappropriate prescriptions (PIP) include Hispanic ethnicity, residing in an assisted care setting, and a greater number of BSH prescriptions prior to admission.[16,19]

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Received: May 24, 2016; **Revised:** October 19, 2016; **Accepted:** November 1, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2739

Additionally, Cumbler et al.[15] found that the presence of dementia was associated with fewer prescriptions for sleep aids in hospital. To our knowledge, there are no published studies that have investigated prescriber factors associated with the use of BSH.

The purpose of our study was to determine the frequency of PIPs of BSH in our academic hospital. Additionally, we aimed to identify patient and prescriber factors that were associated with increased likelihood of prescriptions to help guide future quality improvement initiatives.

METHODS

Study Design and Setting

This was a retrospective observational study conducted at Mount Sinai Hospital (MSH) in Toronto over a 4-month period from January 2013 to April 2013. The hospital is a 442-bed acute care academic health science center affiliated with the University of Toronto. The MSH electronic health record contains demographic data, medications and allergies, nursing documentation, and medical histories from prior encounters. It also includes computerized physician order entry (CPOE) and a detailed medication administration record. This system is integrated with an electronic pharmacy database used to monitor and dispense medications for each patient.

Patient and Medication Selection

We included inpatients over the age of 65 who were prescribed a BSH during the study period from the following services: general internal medicine, cardiology, general surgery, orthopedic surgery, and otolaryngology. To identify new exposure to BSHs, we excluded patients who were regularly prescribed a BSH prior to admission to hospital. The medications of interest included all benzodiazepines and the nonbenzodiazepine sedative hypnotic, zopiclone. Zopiclone is the most commonly used nonbenzodiazepine sedative hypnotic in Canada and the only 1 available on our hospital formulary. These were selected based on the strength of evidence to recommend against their use as first-line agents in older adults and in consultation with our geriatric medicine consultation team pharmacist.[20]

Data Collection

The hospital administrative database provided patient demographic information, admission service, admitting diagnosis, length of stay, and the total number of patients discharged from the study units over the study period. We then searched the pharmacy electronic database for all benzodiazepines and zopiclone prescribed during the study period for patients who met the inclusion criteria. Manual review of paper and electronic health records for this cohort of patients was conducted to extract additional variables. We used a standardized form to record data elements. Dr. Pek collected all data elements. Dr. Remfry reviewed a random sample of patient records (10%) to ensure accuracy. The agreement between reviewers was 100%.

In compliance with hospital accreditation standards, a clinical pharmacist documents a best possible medication history (BPMH) on every inpatient on admission. We used the BPMH to identify and exclude patients who were prescribed a BSH prior to hospitalization. Because all medications were ordered through the CPOE system, as-needed medication prescriptions required the selection of a specified indication. Available options included 'agitation/anxiety' and necessitated combining these 2 indications into 1 category. Indications were primarily extracted through electronic order entry reviews. Paper charts were reviewed when further clarification was needed.

We identified ordering physicians' training level and familiarity with the service from administrative records obtained from medical education offices, hospital records, and relevant call schedules. Fellows were defined as trainees with a minimum of 6 years of postgraduate training.

Variables

Our primary outcome of interest was the proportion of eligible patients age 65 and older who received a PIP for a BSH. Patient variables of interest included age, sex, comorbid conditions, and a pre-admission diagnosis of dementia. Comorbid conditions and age were used to calculate the Carlson Comorbidity Index for each patient.[21] Prescription variables included the medication prescribed, time of first prescription ("overnight hours" refer to prescriptions ordered after 7:00 PM and before 7:00 AM), and whether the medication was ordered as part of an admission or postoperative order set. To determine whether patients were discharged home with a prescription for a BSH, we reviewed electronic discharge prescriptions of BSH-naïve patients who received a sedative in hospital. Only medical and cardiology inpatients receive electronic discharge prescriptions, and these were available for 189 patients in our cohort. Provider variables included training level, service, and familiarity with patients. We used the provider's training program or department of appointment to define the 'physician on-service' variable. As an example, a resident registered in internal medicine is defined as 'on-service' when prescribing sedatives for a medical inpatient. In contrast, a psychiatry resident would be considered "off-service" if he prescribed a sedative for a surgical inpatient. The familiarity of a provider was categorized as 'regular' if they were responsible for a patient's care on a day-to-day basis and 'covering' if they were only covering on call. Other variables included admitting service and hospital length of stay.

Appropriateness Criteria

Criteria for potentially inappropriate use were modified from the American and Canadian Geriatrics Societies' Choosing Wisely recommendations,[4,5] and included insomnia and agitation. These recommendations are in line with other evidence based guidelines for safe prescribing in older adults.[20] For the purposes of our study, prescriptions for "agitation/anxiety", "agitation", or "insomnia/sleep" were considered potentially inappropriate. Appropriate indications included

TABLE 1. Characteristics of Study Patients Newly Prescribed a Benzodiazepine or Sedative Hypnotic In-Hospital

Characteristic	All Patients[a]	Patients Prescribed Appropriate BSH[b]	Patients Prescribed Inappropriate BSH[b]	*P* value
	(n=251)	(n=43)	(n=208)	
Age, mean (95% CI)	79.9 (78.9-81.0)	83.3 (80.8-85.7)	79.2 (78.1-80.3)	0.004
Gender				0.60
Female	131 (52.2%)	24 (18.3%)	107 (81.7%)	
Male	120 (47.8%)	19 (15.8%)	101 (84.2%)	
Admitting diagnosis				0.005
Cardiovascular	64 (25.5%)	9 (14.1%)	55 (85.9%)	
Gastrointestinal	14 (5.6%)	2 (14.3%)	12 (85.7%)	
Injury	29 (11.6%)	4 (13.8%)	25 (86.2%)	
Neoplasm	45 (17.9%)	1 (2.2%)	44 (97.8%)	
Respiratory	18 (7.2%)	3 (16.7%)	15 (83.3%)	
Other	81 (32.3%)	24 (29.6%)	57 (70.4%)	
CCI, mean (95% CI)	6.5 (6.2-6.8)	6.8 (6.0-7.7)	6.4 (6.0-6.7)	0.26
Dementia				0.002
Dementia diagnosis	27 (10.8%)	11 (40.7%)	16 (59.3%)	
No dementia diagnosis	224 (89.2%)	32 (14.3%)	192 (85.7%)	
Service				<0.0001
General internal medicine	126 (50.2%)	37 (29.4%)	89 (70.6%)	
Other (cardiology, surgical)	125 (49.8%)	6 (4.8%)	119 (95.2%)	
Length of stay, mean (95% CI)	12.6 (10.5-14.7)	11.8 (7.7-15.8)	12.8 (10.4-15.1)	0.68

[a]Percentages are column percentages.

[b]Percentages are row percentages.

NOTE: Two-sample t-tests and the Chi-square statistic were used to assess the unadjusted associations of patient-level characteristics with PIP, where appropriate. Abbreviations: BSH, benzodiazepine sedative hypnotic; CCI: Charlson Comorbidity Index; CI, confidence interval.

alcohol withdrawal, end-of-life symptom control, preprocedural sedation, and seizure.[5] Patients who were already using a BSH prior to admission for any indication, including a psychiatric diagnosis, were excluded.

Statistical Analyses

We determined the proportion of patients with at least one PIP, as well as the proportion of all prescribing events that were potentially inappropriate. We used the Chi-square statistic and 2-sample t tests to compare the unadjusted associations between patient-level characteristics and receipt of at least 1 inappropriate prescription and prescribing event-level factors with inappropriate prescriptions. Given that first-year residents are more likely to be working overnight when most PIPs are prescribed, we performed a simple logistic regression of potentially inappropriate prescribing by level of training stratified by time of prescription. A multivariable random-intercept logistic regression model was used to assess the adjusted association between patient- and prescribing event-level characteristics with inappropriate prescribing, adjusting for clustering of prescribing events within patients. Characteristics of interest were identified *a priori* and those with significant bivariate associations with potentially inappropriate were selected for inclusion in the model. Additionally, we included time of prescription in our model to control for potential confounding. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc, Cary, North Carolina). The MSH Research Ethics Board approved the study.

RESULTS

Description of Patients Prescribed a Benzodiazepine Sedative Hypnotic

There were 1540 patients over the age of 65 discharged during the 4-month study period. We excluded the 232 patients who had been prescribed a BSH prior to admission. Of the remaining eligible 1308 BSH-naïve patients, 251 (19.2%) were prescribed a new BSH in hospital and were included in the study. Of this cohort of 251 patients, 193 (76.9%) patients were prescribed a single BSH during their admission while 58 (23.1%) received 2 or more. Of all eligible patients, 208 (15.9%) were prescribed at least 1 PIP. Approximately half of the cohort was admitted to the general internal medicine service, and the most common reason for admission was cardiovascular disease (Table 1).

Description of Prescriptions of Benzodiazepine Sedative Hypnotic

We reviewed 328 prescriptions for BSH during the study period. The majority of these, 254 (77.4%) were potentially

TABLE 2. Provider Characteristics of New In-Hospital Prescriptions and Timing of Prescribing Events

Characteristic	All Prescriptions[a]	Appropriate Prescriptions[b]	Inappropriate Prescriptions[b]	*P* value
	(n=328)	(n=74)	(n=254)	
Physician-training level				0.0007
PGY-1	213 (64.9%)	40 (18.8%)	173 (81.2%)	
PGY-2	36 (11.0%)	16 (44.4%)	20 (55.6%)	
PGY-3-5	53 (16.2%)	8 (15.1%)	45 (84.9%)	
Attending physician and fellows	26 (7.9%)	10 (38.5%)	16 (61.5%)	
Physician service				0.076
On service	225 (68.6%)	57 (25.3%)	168 (74.7%)	
Off service	103 (31.4%)	17 (16.5%)	86 (83.5%)	
Physician familiarity				0.017
Regular	260 (79.3%)	66 (25.4%)	194 (74.6%)	
Covering	68 (20.7%)	8 (11.8%)	60 (88.2%)	
Time of prescription				0.067
Daytime	150 (45.7%)	55 (36.7%)	95 (63.3%)	
Nighttime (7:00 PM to 7:00 AM)	178 (54.3%)	19 (10.7%)	159 (89.3%)	

[a]Percentages are column percentages.

[b]Percentages are row percentages.

NOTE: The Chi-square statistic was used to assess the unadjusted associations between provider characteristics and prescribing event timing with potentially inappropriate prescriptions. Abbreviation: PGY, postgraduate year.

inappropriate (Table 2). The most common PIPs were zopiclone (167; 65.7%) and lorazepam (82; 32.3%). The PIPs were most frequently ordered on an as-needed basis (219; 86%), followed by one-time orders (30; 12%), and standing orders (5; 2%). The majority of PIPs (222; 87.4%) was prescribed for insomnia with a minority (32; 12.6%) prescribed for agitation and/or anxiety.

Most PIP were prescribed during overnight hours (159; 62.6%) and when an in-house pharmacist was unavailable (211; 83.1%). These variables were highly correlated with prescription of sleep aid, which was defined in our criteria as potentially inappropriate. Copies of discharge prescriptions were available for 189 patients. Of these 189 patients, 19 (10.1%) were sent home with a prescription for a new sedative.

Association Between Patient/Provider Variables and Prescriptions

Patient factors associated with fewer PIPs in our bivariate analyses included older age and dementia (Table 1). A greater proportion of nighttime prescriptions were PIPs; however, this finding was not statistically significant ($P = 0.067$). The majority of all prescriptions was prescribed by residents in their first year of training (64.9%; Table 2), and there was a significant difference in rates of PIP across level of training ($P = 0.0007$). When stratified by time of prescription, there was no significant difference by level of training for nighttime prescriptions. Among daytime prescriptions, second-year residents and staff (attending physicians and fellows) were less likely to prescribe a PIP than first-year residents (odds ratio [OR], 0.24; 95% confidence interval [CI], 0.09-0.66 and OR, 0.39; 95% CI, 0.14-1.13, respectively; Table 3); however, the association between staff and first-years only approached statistical significance ($P = 0.08$). Interestingly, 20.4% of all PIPs were ordered routinely as part of an admission or postoperative order set.

In our regression model, admission to a specialty or surgical service, compared to the general internal medicine service, was associated with a significantly higher likelihood of a PIP (OR, 6.61; 95% CI, 2.70-16.17; Table 4). Additionally, compared to cardiovascular admission diagnoses, neoplastic admitting diagnoses were associated with a higher likelihood of a PIP (OR, 4.43; 95% CI, 1.23-15.95). Time of prescription was a significant predictor in our multivariable regression model with nighttime prescriptions having increased odds of a PIP (OR, 4.48; 95% CI, 2.21-9.06,). When comparing prescribers at the extremes of training, attending physicians and fellows were much less likely to prescribe a PIP compared to first-year residents (OR, 0.23; 95% CI, 0.08-0.69; Table 4). However, there were no other significant differences across training levels after adjusting for patient and prescribing event characteristics.

DISCUSSION

We found that the majority of newly prescribed BSH in hospital was for the potentially inappropriate indications of insomnia and agitation/anxiety. Medications for insomnia were primarily initiated during overnight hours. Training level of prescribers and admitting service were found to be associated with appropriateness of prescriptions.

Our study showed that 15.9% of hospitalized older adults were newly prescribed a PIP during their admission. Of all new in hospital prescriptions, 77% were deemed potentially inappropriate. These numbers are similar to those reported

TABLE 3. Associations Between Level of Training with Potentially Inappropriate Prescriptions of Benzodiazepines and Sedative Hypnotics Stratified by Timing of Prescription

Timing of Prescription	Reference Level of Training	Comparison Level of Training	OR (95% CI)	*P* value
Daytime (7:00 AM to 7:00 PM)	PGY-1	PGY-2	0.24 (0.09-0.66)	0.0061
		PGY-3-5	1.40 (0.50-3.90)	0.52
		Attending physicians and fellows	0.39 (0.14-1.13)	0.08
Nighttime (7:00 PM to 7:00 AM)	PGY-1	PGY-2	0.50 (0.13-2.00)	0.33
		PGY-3-5	1.51 (0.32-7.10)	0.61
		Attending physicians and fellows	0.93 (0.11-8.03)	0.95

NOTE: Effect size estimates were calculated using simple logistic regression for the association between level of training with potentially inappropriate prescription stratified by timing of prescription. Abbreviations: CI, confidence interval; OR, odds ratio.

TABLE 4. Association of Patient and Prescription Characteristics with Potentially Inappropriate Prescriptions of Benzodiazepines and Sedative Hypnotics

Characteristics	Reference Group	Comparison Group	OR (95% CI)	*P* value
Admitting diagnosis	Circulatory	Neoplasm	4.43 (1.23-15.95)	0.023[a]
		Other	1.60 (0.64-3.95)	0.31
Age, grouped	65-79 y	≥80 y	1.05 (0.50-2.21)	0.90
Dementia	Dementia diagnosis	No dementia diagnosis	1.79 (0.67-4.83)	0.25
Familiarity with patient	Regular	Covering	1.22 (0.42-3.57)	0.72
Hospital service	General internal medicine	Other (surgical, cardiology)	6.61 (2.70-16.17)	<0.001[a]
Time of prescription	Daytime	Nighttime	4.48 (2.21-9.06)	<0.001[a]
Training	PGY-1	PGY-2	0.52 (0.30-1.33)	0.17
		PGY-3-5	0.91 (0.30-2.77)	0.87
		Attending physicians and fellows	0.28 (0.08-0.93)	0.037[a]

[a]Denotes statistical significance at $P < 0.05$.

NOTE: A multivariable random-intercept logistic regression model was used to assess the adjusted associations between patient- and prescribing event-level characteristics with inappropriate prescribing, adjusting for clustering of prescribing events within patients. Abbreviations: CI, confidence interval; OR, odds ratio; PGY, postgraduate year.

by other centers; however, wide ranges exist.[16,19] This is likely the result of differences in appropriate use and inclusion criteria. Gillis et al.[17] focused their investigation on sleep aids and showed that 26% of all admitted patients and 18% of BSH naïve patients received a prescription for insomnia. While this is similar to our findings, more than half of these patients were under the age of 65, and additional medications, such as trazodone, antihistamines, and antipsychotics were included.[17] Other studies did not exclude patients who used a BSH regularly prior to admission. For example, 21% of veterans admitted to an acute care facility received a prescription for potentially inappropriate indications, but this included continuation of prior home medications.[19] In contrast, we chose to focus on older adults in whom BSH pose a greater risk of harm. Exclusion of patients who regularly used a BSH prior to admission allowed us to better understand the circumstances surrounding the initiation of these medications in hospital. Furthermore, abrupt cessation of benzodiazepines can cause withdrawal and worsen confusion.[22]

We found that 10% of patients newly prescribed a BSH in hospital were discharged with a prescription for a BSH. The accuracy of this is limited by the lack of availability of electronic discharge prescriptions on our surgical wards; however, it is likely an underrepresentation of the true effect given the high rates of PIPs on these wards. Our study highlights the concerning practice of continuing newly prescribed BSH following discharge from hospital.

Sleep disruption and poor quality sleep in hospital is a common issue that leads to significant use of BSH.[15] Nonpharmacologic interventions in older adults can be effective in improving sleep quality and reducing the need for BSH; however, they can be time-consuming to implement.[23] With the exception of preventative strategies used on our Acute Care for Elders unit, formal nonpharmacologic interventions for sleep are not practiced in our hospital. We found that the majority of PIPs were prescribed as sleep aids in the overnight hours. This suggests that disruptions in sleep are leading patients and nursing staff to request pharmacologic treatments and highlights an area with significant room for improvement. Work is underway to

implement and evaluate safe sleep protocols for older adults.

To our knowledge, we are the first to report an association between training level and PIP of BSH in older adults. The highest rates of PIPs were found among the first-year residents and, after controlling for patient and prescribing event characteristics, such as time of prescription, first-year residents were significantly more likely to prescribe a PIP. First-year residents are more likely to respond first to issues on the wards. There may be pressure on first-year trainees to prescribe sleep aids, as many patients and nurses may seek pharmacologic solutions for symptom management. Knowledge gaps may also be a contributing factor early in their training. A survey of physicians found that residents were more likely than attending physicians to list lack of formal education as a barrier to appropriate prescribing.[24]

Similarities are seen in a study of antibiotic appropriateness, where residents demonstrated gaps in knowledge of treatment of asymptomatic bacteriuria that seemed to vary by specialty.[25] Interestingly, we found that patients admitted to general internal medicine were prescribed fewer PIPs. This service includes our Acute Care for Elders unit, which is staffed by trained geriatric nurses and other allied health professionals. Residents who rotated on internal medicine are also likely to have received informal teaching about medication safety in older adults. Educational interventions highlighting adverse effects of BSH and promoting nonpharmacologic solutions should be targeted at first-year residents. However, an interprofessional team approach to sleep disturbance in hospital, in combination with decision support for appropriate BSH use will achieve greater impact than education alone.

Several limitations of this study merit discussion. First, findings from a single academic center may lack generalizability. However, the demographics of our patient population and our rates of BSH use were similar to those reported in previous studies. Second, our study may be subject to observer bias, as the data collectors were not blinded. To minimize this, a strict template and clear appropriateness criteria were developed. Additionally, a second reviewer independently conducted data validation with 100% agreement among reviewers. Third, we studied prescribing patterns rather than medication administration and lacked data on filling of new BSH prescriptions in the postdischarge period. However, our primary goal is to determine risk of exposure to a BSH to minimize it. Fourth, although BSH are discouraged as "first choice for insomnia, anxiety or delirium,"[4] they may be appropriate in limited situations where all nonpharmacologic strategies have failed and patient or staff safety is at risk. In our chart reviews, we were unable to determine whether all nonpharmacologic strategies were exhausted prior to prescription initiation. However, more than 20% of all PIP were routinely prescribed as part of an admission or postoperative order set, suggesting a reflexive rather than reflective approach to sedative use. Furthermore, the indications of anxiety and agitation were combined as they appear in the CPOE as a combination indication, thus leaving us unable to determine the true proportion for each indication. However, more than 87% of all PIPs were for insomnia, reflecting a clear opportunity to improve sleep management in hospital. Last, the lack of a power calculation may have resulted in the study being underpowered and thus affected the ability to detect a significant effect of covariates that have real differences on the likelihood of sedative prescriptions. For example, the low number of prescribing events by second-year residents and staff may have resulted in a type II error when comparing PIP rates with first-year residents.

We found that the majority of newly prescribed BSH among older adults in hospital were potentially inappropriate. They were most frequently prescribed by first-year residents overnight in response to insomnia. Our findings demonstrate BSH overuse remains prevalent and is associated with poor sleep in hospital. Future work will focus on implementing and evaluating safe sleep protocols and educational interventions aimed at first-year residents.

Acknowledgments

Elisabeth Pek 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. Ciara Pendrith conducted and is responsible for the statistical analysis.

Disclosure: The authors report no financial conflicts of interest.

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Incidence, Predictors, and Outcomes of Hospital-Acquired Anemia

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BACKGROUND: Although hypothesized to be a hazard of hospitalization, it is unclear whether hospital-acquired anemia (HAA) is associated with increased adverse outcomes following discharge.

OBJECTIVE: To examine the incidence, predictors, and postdischarge outcomes associated with HAA.

DESIGN: Observational cohort study using electronic health record data.

SUBJECTS: Consecutive medicine discharges between November 1, 2009 and October 30, 2010 from 6 Texas hospitals, including safety-net, teaching, and nonteaching sites. Patients with anemia on admission or missing hematocrit values at admission or discharge were excluded.

MEASURES: HAA was defined using the last hematocrit value prior to discharge and categorized by severity. The primary outcome was a composite of 30-day mortality and nonelective readmission.

RESULTS: Among 11,309 patients, one-third developed HAA (21.6% with mild HAA; 10.1% with moderate HAA; and 1.4% with severe HAA). The 2 strongest potentially modifiable predictors of developing moderate or severe HAA were length of stay (adjusted odds ratio [OR], 1.26 per day; 95% confidence interval [CI], 1.23-1.29) and receipt of a major procedure (adjusted OR, 5.09; 95% CI, 3.79-6.82). Patients without HAA had a 9.7% incidence for the composite outcome versus 16.4% for those with severe HAA. Severe HAA was independently associated with a 39% increase in the odds for 30-day readmission or death (95% CI, 1.09-1.78). Most patients with severe HAA (85%) underwent a major procedure, had a discharge diagnosis of hemorrhage, and/or a discharge diagnosis of hemorrhagic disorder.

CONCLUSIONS: Severe HAA is associated with increased odds for 30-day mortality and readmission after discharge; however, it is uncertain whether severe HAA is preventable. *Journal of Hospital Medicine* 2017;12:317-322. © 2017 Society of Hospital Medicine

Hospital-acquired anemia (HAA) is defined as having a normal hemoglobin value upon admission but developing anemia during the course of hospitalization. The condition is common, with an incidence ranging from approximately 25% when defined by using the hemoglobin value prior to discharge to 74% when using the nadir hemoglobin value during hospitalization.[1-5] While there are many potential etiologies for HAA, given that iatrogenic blood loss from phlebotomy may lead to its development,[6,7] HAA has been postulated to be a hazard of hospitalization that is potentially preventable.[8] However, it is unclear whether the development of HAA portends worse outcomes after hospital discharge.

The limited number of studies on the association between HAA and postdischarge outcomes has been restricted to patients hospitalized for acute myocardial infarction (AMI).[3,9,10] Among this subpopulation, HAA is independently associated with greater morbidity and mortality following hospital discharge.[3,9,10] In a more broadly representative population of hospitalized adults, Koch et al.[2] found that the development of HAA is associated with greater length of stay (LOS), hospital charges, and inpatient mortality. However, given that HAA was defined by the lowest hemoglobin level during hospitalization (and not necessarily the last value prior to discharge), it is unclear if the worse outcomes observed were the cause of the HAA, rather than its effect, since hospital LOS is a robust predictor for the development of HAA, as well as a major driver of hospital costs and a prognostic marker for inpatient mortality.[3,9] Furthermore, this study evaluated outcomes only during the index hospitalization, so it is unclear if patients who develop HAA have worse clinical outcomes after discharge.

Therefore, in this study, we used clinically granular electronic health record (EHR) data from a diverse cohort of consecutive medicine inpatients hospitalized for any reason at 1 of 6 hospitals to: 1) describe the epidemiology of HAA; 2) identify predictors of its development; and 3) examine its association with 30-day postdischarge adverse outcomes. We hypothesized that the development of HAA would be independently associated with 30-day readmission and mortality in a dose-dependent fashion, with increasing severity of HAA associated with worse outcomes.

METHODS

Study Design, Population, and Data Sources

We conducted a retrospective observational cohort study using EHR data collected from November 1, 2009 to Oc-

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Additional Supporting Information may be found in the online version of this article.

Received: August 16, 2016; **Revised:** October 24, 2016; **Accepted:** November 3, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2723

tober 30, 2010 from 6 hospitals in the north Texas region. One site was a university-affiliated safety-net hospital; the remaining 5 community hospitals were a mix of teaching and nonteaching sites. All hospitals used the Epic EHR system (Epic Systems Corporation, Verona, Wisconsin). Details of this cohort have been published.[11,12]

This study included consecutive hospitalizations among adults age 18 years or older who were discharged from a medicine inpatient service with any diagnosis. We excluded hospitalizations by individuals who were anemic within the first 24 hours of admission (hematocrit less than 36% for women and less than 40% for men), were missing a hematocrit value within the first 24 hours of hospitalization or a repeat hematocrit value prior to discharge, had a hospitalization in the preceding 30 days (ie, index hospitalization was considered a readmission), died in the hospital, were transferred to another hospital, or left against medical advice. For individuals with multiple eligible hospitalizations during the study period, we included only the first hospitalization. We also excluded those discharged to hospice, given that this population of individuals may have intentionally desired less aggressive care.

Definition of Hospital-Acquired Anemia

HAA was defined as having a normal hematocrit value (36% or greater for women and 40% or greater for men) within the first 24 hours of admission and a hematocrit value at the time of hospital discharge lower than the World Health Organization's sex-specific cut points.[13] If there was more than 1 hematocrit value on the same day, we chose the lowest value. Based on prior studies, HAA was further categorized by severity as mild (hematocrit greater than 33% and less than 36% in women; and greater than 33% and less than 40% in men), moderate (hematocrit greater than 27% and 33% or less for all), or severe (hematocrit 27% or less for all).[2,14]

Characteristics

We extracted information on sociodemographic characteristics, comorbidities, LOS, procedures, blood transfusions, and laboratory values from the EHR. Hospitalizations in the 12 months preceding the index hospitalization were ascertained from the EHR and from an all-payer regional hospitalization database that captures hospitalizations from 75 acute care hospitals within a 100-mile radius of Dallas-Fort Worth. *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* discharge diagnosis codes were categorized according to the Agency for Healthcare Research and Quality (AHRQ) Clinical Classifications Software (CCS).[15] We defined a diagnosis for hemorrhage and coagulation, and hemorrhagic disorder as the presence of any ICD-9-CM code (primary or secondary) that mapped to the AHRQ CCS diagnoses 60 and 153, and 62, respectively. Procedures were categorized as minor diagnostic, minor therapeutic, major diagnostic, and major therapeutic using the AHRQ Healthcare Cost and Utilization Procedure Classes tool.[16]

Outcomes

The primary outcome was a composite of death or readmission within 30 days of hospital discharge. Hospital readmissions were ascertained at the index hospital and at any of 75 acute care hospitals in the region as described earlier. Death was ascertained from each of the hospitals' EHR and administrative data and the Social Security Death Index. Individuals who had both outcomes (eg, a 30-day readmission and death) were considered to have only 1 occurrence of the composite primary outcome measure. Our secondary outcomes were death and readmission within 30 days of discharge, considered as separate outcomes.

Statistical Analysis

We used logistic regression models to evaluate predictors of HAA and to estimate the association of HAA on subsequent 30-day adverse outcomes after hospital discharge. All models accounted for clustering of patients by hospital. For the outcomes analyses, models were adjusted for potential confounders based on prior literature and our group's expertise, which included age, sex, race/ethnicity, Charlson comorbidity index, prior hospitalizations, nonelective admission status, creatinine level on admission, blood urea nitrogen (BUN) to creatinine ratio of more than 20:1 on admission, LOS, receipt of a major diagnostic or therapeutic procedure during the index hospitalization, a discharge diagnosis for hemorrhage, and a discharge diagnosis for a coagulation or hemorrhagic disorder. For the mortality analyses, given the limited number of 30-day deaths after hospital discharge in our cohort, we collapsed moderate and severe HAA into a single category. In sensitivity analyses, we repeated the adjusted model, but excluded patients in our cohort who had received at least 1 blood transfusion during the index hospitalization (2.6%) given its potential for harm, and patients with a primary discharge diagnosis for AMI (3.1%).[17]

The functional forms of continuous variables were assessed using restricted cubic splines and locally weighted scatterplot smoothing techniques. All analyses were performed using STATA statistical software version 12.0 (StataCorp, College Station, Texas). The University of Texas Southwestern Medical Center institutional review board approved this study.

RESULTS

Of 53,995 consecutive medicine hospitalizations among adults age 18 years or older during our study period, 11,309 index hospitalizations were included in our study cohort (Supplemental Figure 1). The majority of patients excluded were because of having documented anemia within the first 24 hours of admission (n=24,950). With increasing severity of HAA, patients were older, more likely to be female, non-Hispanic white, electively admitted, have fewer comorbidities, less likely to be hospitalized in the past year, more likely to have had a major procedure, receive a blood transfusion, have a longer LOS, and have a primary or secondary discharge diagnosis for a hemorrhage or a coagulation or hemorrhagic disorder (Table 1).

Epidemiology of HAA

Among this cohort of patients without anemia on admission, the median hematocrit value on admission was 40.6 g/dL and on discharge was 38.9 g/dL. One-third of patients with normal hematocrit value at admission developed HAA, with 21.6% developing mild HAA, 10.1% developing moderate HAA, and 1.4% developing severe HAA. The median discharge hematocrit value was 36 g/dL (interquartile range [IQR]), 35-38 g/dL) for the group of patients who developed mild HAA, 31 g/dL (IQR, 30-32 g/dL) for moderate HAA, and 26 g/dL (IQR, 25-27 g/dL) for severe HAA (Supplemental Figure 2). Among the severe HAA group, 135 of the 159 patients (85%) had a major procedure (n=123, accounting for 219 unique major procedures), a diagnosis for hemorrhage (n=30), and/or a diagnosis for a coagulation or hemorrhagic disorder (n=23) during the index hospitalization. Of the 219 major procedures among patients with severe HAA, most were musculoskeletal (92 procedures), cardiovascular (61 procedures), or digestive system-related (41 procedures). The most common types of procedures were coronary artery bypass graft (36 procedures), hip replacement (25 procedures), knee replacement (17 procedures), and femur fracture reduction (15 procedures). The 10 most common principal discharge diagnoses of the index hospitalization by HAA group are shown in Supplemental Table 1. For the severe HAA group, the most common diagnosis was hip fracture (20.8%).

Predictors of HAA

Compared to no or mild HAA, female sex, elective admission status, serum creatinine on admission, BUN to creatinine ratio greater than 20 to 1, hospital LOS, and undergoing a major diagnostic or therapeutic procedure were predictors for the development of moderate or severe HAA (Table 2). The model explained 23% of the variance (McFadden's pseudo R^2).

Incidence of Postdischarge Outcomes by Severity of HAA

The severity of HAA was associated with a dose-dependent increase in the incidence of 30-day adverse outcomes, such that patients with increasing severity of HAA had greater 30-day composite, mortality, and readmission outcomes ($P <$ 0.001; Figure). The 30-day postdischarge composite outcome was primarily driven by hospital readmissions given the low mortality rate in our cohort. Patients who did not develop HAA had an incidence of 9.7% for the composite outcome, whereas patients with severe HAA had an incidence of 16.4%. Among the 24 patients with severe HAA but who had not undergone a major procedure or had a discharge diagnosis for hemorrhage or for a coagulation or hemorrhagic disorder, only 3 (12.5%) had a composite postdischarge adverse outcome (2 readmissions and 1 death). The median time to readmission was similar between groups, but more patients with severe HAA had an early readmission within 7 days of hospital discharge than patients who did not develop HAA (6.9% vs. 2.9%, P = 0.001; Supplemental Table 2).

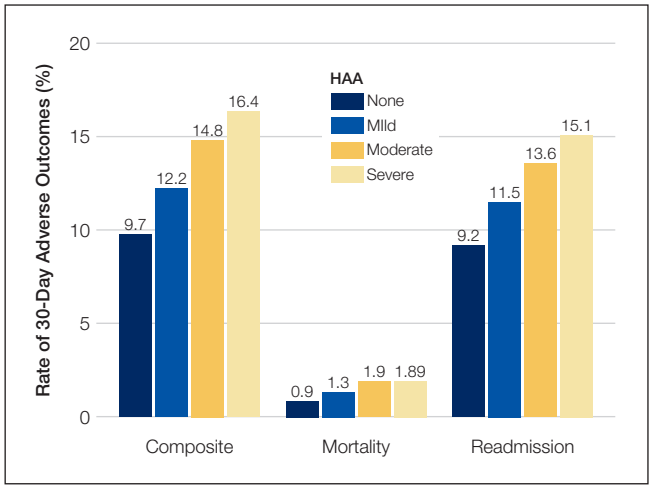

FIG. Incidence of adverse outcomes by severity of HAA. The *P* values for the differences in the 30-day composite, mortality, and readmission outcomes by HAA severity were <0.001, 0.004, and <0.001, respectively.

NOTE: Abbreviation: HAA, hospital-acquired anemia.

Association of HAA and Postdischarge Outcomes

In unadjusted analyses, compared to not developing HAA, mild, moderate, and severe HAA were associated with a 29%, 61%, and 81% increase in the odds for a composite outcome, respectively (Table 3). After adjustment for confounders, the effect size for HAA attenuated and was no longer statistically significant for mild and moderate HAA. However, severe HAA was significantly associated with a 39% increase in the odds for the composite outcome and a 41% increase in the odds for 30-day readmission (P = 0.008 and P = 0.02, respectively).

In sensitivity analyses, the exclusion of individuals who received at least 1 blood transfusion during the index hospitalization (n=298) and individuals who had a primary discharge diagnosis for AMI (n=353) did not substantively change the estimates of the association between severe HAA and postdischarge outcomes (Supplemental Tables 3 and 4). However, because of the fewer number of adverse events for each analysis, the confidence intervals were wider and the association of severe HAA and the composite outcome and readmission were no longer statistically significant in these subcohorts.

DISCUSSION

In this large and diverse sample of medical inpatients, we found that HAA occurs in one-third of adults with normal hematocrit value at admission, where 10.1% of the cohort developed moderately severe HAA and 1.4% developed severe HAA by the time of discharge. Length of stay and undergoing a major diagnostic or therapeutic procedure were the 2 strongest potentially modifiable predictors of developing moderate or severe HAA. Severe HAA was independently associated with a 39% increase in the odds of being readmitted or dying within 30 days after hospital discharge compared to not developing HAA. However, the

TABLE 1. Baseline Characteristics of Hospitalized Medicine Patients (N=11,309)

	HAA Severity[a]				
	None	Mild	Moderate	Severe	*P*
N	7563	2445	1142	159	
Age, mean (SD), y	59.6 (17.1)	59.7 (17.5)	63.3 (16.9)	65.3 (16.0)	<0.001
Female, n (%)	4487 (59.3)	1188 (48.6)	948 (83.0)	114 (71.7)	<0.001
Race/ethnicity, n (%)					0.002
White	5109 (67.6)	1570 (64.2)	808 (70.8)	122 (76.7)	
Black	1261 (16.7)	448 (18.3)	174 (15.2)	13 (8.2)	
Hispanic	949 (12.5)	344 (14.1)	128 (11.2)	18 (11.3)	
Other	244 (3.2)	83 (3.4)	32 (2.8)	6 (3.8)	
Primary insurance, n (%)					<0.001
Private	3186 (42.1)	924 (37.8)	446 (39.1)	58 (36.5)	
Medicare	2574 (34.0)	875 (35.8)	485 (42.5)	79 (49.7)	
Other	1803 (23.8)	646 (26.4)	211 (18.5)	22 (13.8)	
Nonelective admission, n (%)	6884 (91.0)	2172 (88.8)	916 (80.2)	122 (76.7)	<0.001
Charlson Comorbidity Index, n (%)					<0.001
0	6030 (79.7)	1842 (75.3)	862 (75.5)	131 (82.4)	
1+	1533 (20.3)	603 (24.7)	280 (24.5)	28 (17.6)	
≥1 hospitalizations in past y, n (%)	1885 (24.9)	736 (30.1)	329 (28.8)	32 (20.1)	<0.001
Hematocrit on admission, median (IQR)	41 (39-43)	41 (38-42)	38 (37-41)	39 (37-42)	<0.001
Prothrombin time >35 on admission, n (%)	73 (0.97)	25 (1.02)	9 (0.79)	1 (0.63)	0.887
Platelets <100 x 10^3/μL on admission, n (%)	155 (2.05)	56 (2.29)	31 (2.71)	2 (1.26)	0.406
Creatinine, mean (SD), mg/dL	1.15 (1.01)	1.34 (1.26)	1.38 (1.30)	1.34 (1.16)	<0.001
BUN to creatinine >20:1 on admission, n (%)	2168 (28.7)	711 (29.1)	410 (35.9)	70 (44.0)	<0.001
Procedures, n (%)[b]					<0.001
None	4021 (53.2)	929 (38.0)	257 (22.5)	4 (2.5)	
Minor diagnostic	1277 (16.9)	293 (12.0)	61 (5.4)	3 (1.9)	
Minor therapeutic	1505 (19.9)	639 (26.1)	272 (23.8)	29 (18.2)	
Major diagnostic	57 (0.7)	33 (1.4)	16 (1.4)	0 (0)	
Major therapeutic	703 (9.3)	551 (22.5)	536 (46.9)	123 (77.4)	
Receipt of blood transfusion, n (%)	44 (0.6)	75 (3.1)	136 (11.9)	43 (27.0)	<0.001
LOS, median (IQR), d	3 (2-5)	4 (3-7)	6 (4-10)	8 (5-12)	<0.001
Any discharge diagnoses, n (%)[c]					
Hemorrhage	64 (0.9)	48 (1.96)	83 (7.3)	30 (18.9)	<0.001
Coagulation or hemorrhagic disorder	264 (3.5)	146 (6.0)	84 (7.4)	23 (14.5)	<0.001

[a]HAA was categorized by severity as mild (hematocrit >33% and <36% in women; and >33% and <40% in men), moderate (hematocrit >27% and ≤33% for all), or severe (hematocrit ≤27% for all).

[b]Categorized according to the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project's Procedure Classes. If >1 procedure during the hospitalization, it was classified according to the most invasive one.

[c]Defined by a primary or secondary discharge ICD-9-CM code categorized by the Agency for Healthcare Research and Quality Clinical Classifications software.

NOTE: Abbreviations: BUN, blood urea nitrogen; HAA, hospital-acquired anemia; IQR, interquartile range; LOS, length of stay; SD, standard deviation.

associations between mild or moderate HAA with adverse outcomes were attenuated after adjusting for confounders and were no longer statistically significant.

To our knowledge, this is the first study on the postdischarge adverse outcomes of HAA among a diverse cohort of medical inpatients hospitalized for any reason. In a more restricted population, Salisbury et al.[3] found that patients hospitalized for AMI who developed moderate to severe HAA (hemoglobin value at discharge of 11 g/dL or less) had greater 1-year mortality than those without HAA (8.4% vs. 2.6%, $P < 0.001$), and had an 82% increase in the hazard for mortality (95% confidence interval, hazard ratio 1.11-2.98). Others have similarly shown that HAA is common among patients hospitalized with AMI and is associated with greater mortality.[5,9,18] Our study extends upon this prior research by showing that severe HAA increases the risk for adverse outcomes for all adult inpatients, not only those hospitalized for AMI or among those receiving blood transfusions.

Despite the increased harm associated with severe HAA, it is unclear whether HAA is a preventable hazard of hospitalization, as suggested by others.[6,8] Most patients in our cohort who developed severe HAA underwent a major procedure, had a discharge diagnosis for hemorrhage, and/or had a discharge diagnosis for a coagulation or hemorrhagic disorder. Thus, blood loss due to phlebotomy, 1 of the more modifiable etiologies of HAA, was unlikely to have been the primary driver for most patients who developed severe HAA. Since it has been estimated to take 15 days of daily phlebotomy of 53 mL of whole blood in females of average body weight (and 20 days for average weight males) with

no bone marrow synthesis for severe anemia to develop, it is even less likely that phlebotomy was the principal etiology given an 8-day median LOS among patients with severe HAA.[19,20] However, since the etiology of HAA can be multifactorial, limiting blood loss due to phlebotomy by using smaller volume tubes, blood conservation devices, or reducing unnecessary testing may mitigate the development of severe HAA.[21,22] Additionally, since more than three-quarters of patients who developed severe HAA underwent a major procedure, more care and attention to minimizing operative blood loss could lessen the severity of HAA and facilitate better recovery. If minimizing blood loss is not feasible, in the absence of symptoms related to anemia or ongoing blood loss, randomized controlled trials overwhelmingly support a restrictive transfusion strategy using a hemoglobin value threshold of 7 mg/dL, even in the postoperative setting.[23-25]

The implications of mild to moderate HAA are less clear. The odds ratios for mild and moderate HAA, while not statistically significant, suggest a small increase in harm compared to not developing HAA. Furthermore, the upper boundary of the confidence intervals for mild and moderate HAA cannot exclude a possible 30% and 56% increase in the odds for the 30-day composite outcome, respectively. Thus, a better powered study, including more patients and extending the time interval for ascertaining postdischarge adverse events beyond 30 days, may reveal a harmful association. Lastly, our study assessed only the association of HAA with 30-day readmission and mortality. Examining the association between HAA and other patient-centered outcomes such as fatigue, functional impairment, and prolonged post-hospitalization recovery time may uncover other important adverse effects of mild and moderate HAA, both of which occur far more frequently than severe HAA.

Our findings should be interpreted in the context of several limitations. First, although we included a diverse group of patients from a multihospital cohort, generalizability to other settings is uncertain. Second, as this was a retrospective study using EHR data, we had limited information to infer the precise mechanism of HAA for each patient. However, procedure codes and discharge diagnoses enabled us to assess which patients underwent a major procedure or had a hemorrhage or hemorrhagic disorder during the hospitalization. Third, given the relatively few number of patients with severe HAA in our cohort, we were unable to assess if the association of severe HAA differed by suspected etiology. Lastly, because we were unable to ascertain the timing of the hematocrit values within the first 24 hours of admission, we excluded both patients with preexisting anemia on admission and those who developed HAA within the first 24 hours of admission, which is not uncommon.[26] Thus, we were unable to assess the effect of acute on chronic anemia arising during hospitalization and HAA that develops within the first 24 hours, both of which may also be harmful.[18,27,28]

In conclusion, severe HAA occurs in 1.4% of all medical hospitalizations and is associated with increased odds of death or readmission within 30 days. Since most patients

TABLE 2. Predictors of Developing Moderate or Severe HAA

	Adjusted OR (95% CI)
Age, per 10 years	1.05 (0.95-1.17)
Female	3.84 (2.65-5.57)
Race/ethnicity	
White	[Reference]
Black	1.01 (0.90-1.14)
Hispanic	1.12 (0.89-1.41)
Other	0.97 (0.75-1.27)
Charlson Comorbidity Index	0.99 (0.87-1.12)
Prior hospitalizations, per admission	1.01 (0.97-1.06)
Elective admission status	1.52 (1.36-1.70)
Creatinine, per 0.5 mg/dL	1.08 (1.04-1.13)
BUN to creatinine ratio >20:1	1.23 (1.03-1.46)
Length of stay, per day	1.26 (1.23-1.29)
Major diagnostic or therapeutic procedure	5.09 (3.79-6.82)

NOTE: Abbreviations: BUN, blood urea nitrogen; CI, confidence interval; HAA, hospital-acquired anemia; OR, odds ratio.

TABLE 3. Association of HAA and 30-Day Postdischarge Adverse Outcomes[a]

	HAA Severity			
Outcome and model	None	Mild	Moderate	Severe
Composite				
Unadjusted	[Reference]	1.29 (1.11-1.48)	1.61 (1.23-2.10)	1.81 (1.28-2.56)
Adjusted[b]	[Reference]	1.08 (0.90-1.30)	1.17 (0.87-1.56)	1.39 (1.09-1.78)
Readmission				
Unadjusted	[Reference]	1.28 (1.11-1.48)	1.55 (1.16-2.08)	1.76 (1.17-2.65)
Adjusted[b]	[Reference]	1.11 (0.94-1.31)	1.16 (0.85-1.57)	1.41 (1.05-1.91)
Mortality		Mild	Moderate/Severe	
Unadjusted	[Reference]	1.53 (0.99-2.37)	2.26 (1.75-2.92)	
Adjusted[b]	[Reference]	0.97 (0.57-1.65)	1.34 (0.88-2.04)	

[a]All models accounted for clustering of patients by hospital. Values shown are odds ratios (95% confidence interval).

[b]Adjusted for age, sex, race/ethnicity, Charlson Comorbidity Index, prior hospitalizations in past year, nonelective admission status, LOS, creatinine on admission, blood urea nitrogen to creatinine ratio >20:1 on admission, receipt of a major diagnostic and/or therapeutic procedure during the index hospitalization, a discharge diagnosis for hemorrhage, and a discharge diagnosis for a coagulation or hemorrhagic disorder.

NOTE: Abbreviations: HAA, hospital-acquired anemia; LOS, length of stay.

with severe HAA had undergone a major procedure or had a discharge diagnosis of hemorrhage or a coagulation or hemorrhagic disorder, it is unclear if severe HAA is potentially preventable through preventing blood loss from phlebotomy or by reducing iatrogenic injury during procedures. Future research should assess the potential preventability of severe HAA, and examine other patient-centered outcomes potentially related to anemia, including fatigue, functional impairment, and trajectory of posthospital recovery.

Acknowledgments

The authors would like to acknowledge Ruben Amarasingham, MD, MBA, President and Chief Executive Officer of the Parkland Center for Clinical Innovation, and Ferdinand Velasco, MD, Chief Health Information Officer at Texas Health Resources, for their assistance in assembling the 6 hospital cohort used in this study. The authors would also like to thank Valy Fontil, MD, MAS, Assistant Professor of Medicine at the University of California San Francisco School of Medicine, and Elizabeth Rogers, MD, MAS, Assistant Professor of Internal Medicine and Pediatrics at the University of Minnesota Medical School, for their constructive feedback on an earlier version of this manuscript.

Disclosures: This work was supported by the Agency for Healthcare Research and Quality-funded UT Southwestern Center for Patient-Centered Outcomes Research (R24 HS022418-01); the Commonwealth Foundation (#20100323); the UT Southwestern KL2 Scholars Program supported by the National Institutes of Health (KL2 TR001103); the National Center for Advancing Translational Sciences at the National Institute of Health (U54 RFA-TR-12-006); and the National Institute on Aging (K23AG052603). The study sponsors had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript. The authors have no financial conflicts of interest to disclose.

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Association Between Radiologic Incidental Findings and Resource Utilization in Patients Admitted With Chest Pain in an Urban Medical Center

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BACKGROUND: Increasing use of testing among hospitalized patients has resulted in an increase in radiologic incidental findings (IFs), which challenge the provision of high-value care in the hospital setting.

OBJECTIVE: To understand impact of radiologic incidental findings on resource utilization in patients hospitalized with chest pain.

DESIGN: Retrospective observational cross sectional study.

SETTING: Academic medical center.

PARTICIPANTS: Adult patients hospitalized with principal diagnosis of chest pain.

MEASUREMENTS: Demographic, imaging, and length of stay (LOS) data were abstracted from the medical charts. We used multiple logistic regression to evaluate factors associated with radiologic IFs and negative binomial regression to evaluate the association between radiologic IFs and LOS.

RESULTS: 1811 consecutive admissions with chest pain were analyzed retrospectively over a period of 24 months; 376 patients were included in the study after exclusion criteria were applied and readmissions removed. Of these, 197 patients (52%) had 364 new radiologic IFs on imaging; most IFs were of minor (50%) or moderate clinical significance (42%), with only 7% of major significance. Odds of finding radiologic IFs increased with age (adjusted odds ratio, 1.04; 95% confidence interval [CI], 1.01-1.06) and was associated with a 26% increase in LOS (adjusted incidence rate ratio, 1.26; 95% CI, 1.07-1.49).

CONCLUSION: Radiologic IFs were very common among patients hospitalized with chest pain of suspected cardiac origin and independently associated with an increase in the LOS. Interventions to address radiologic IFs may reduce LOS and, thereby, support high-value care. *Journal of Hospital Medicine* 2017;12:323-328. © 2017 Society of Hospital Medicine

Diagnostic imaging is an integral part of patient evaluation in acute care settings. The use of imaging for presenting complaints of chest pain, abdominal pain, and injuries has increased in emergency departments across the United States without an increase in detection of acute pathologic conditions.[1,2] An unintended consequence of this increase in diagnostic imaging is the discovery of incidental findings (IFs).

Incidental findings are unexpected findings (eg, nodules) noted on diagnostic imaging that are not related to the presenting complaint.[3] The increasing use of diagnostic imaging and increased sensitivity of these tests have led to a higher burden of radiologic IFs.[4] In a tertiary level hospital, Lumbreras et al.[5] found that the overall incidence of IFs for all radiologic imaging for inpatients and outpatients was 15%, while Orme et al.[6] found that the incidence in imaging research was 39.8%. The existing evidence base suggests that the identification of radiologic IFs has financial,[5,7] clinical,[6] ethical, and legal implications.[8] Also, IFs increase workload for healthcare professionals, including that related to follow-up and surveillance.[9]

In the field of radiology, the burden of radiologic IFs is a well-accepted fact and various white papers have been published by the American College of Radiology on how to address them.[4,7] Hospitalized patients are a population that undergoes a substantial number of diagnostic tests. In the era of accountable care organizations[10] with an emphasis on population health and high-value care, radiologic IFs pose a particular challenge to healthcare providers.

Chest pain is one of the most common reasons for emergency department visits in the United States.[11] In this study, we report on radiologic IFs and factors associated with these among patients hospitalized for chest pain of suspected cardiac origin, and we evaluate the hypothesis that radiologic IFs are associated with an increase in LOS in this population.

METHODS

We conducted a secondary analysis of data from the Chest Pain and Cocaine Study (CPAC). The CPAC study is a cross sectional study of all patients hospitalized with chest pain to our urban academic medical center. Medical records were reviewed to generate a database of all such patients during

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Additional Supporting Information may be found in the online version of this article.

Received: July 12, 2016; **Revised:** November 5, 2016; **Accepted:** November 13, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2722

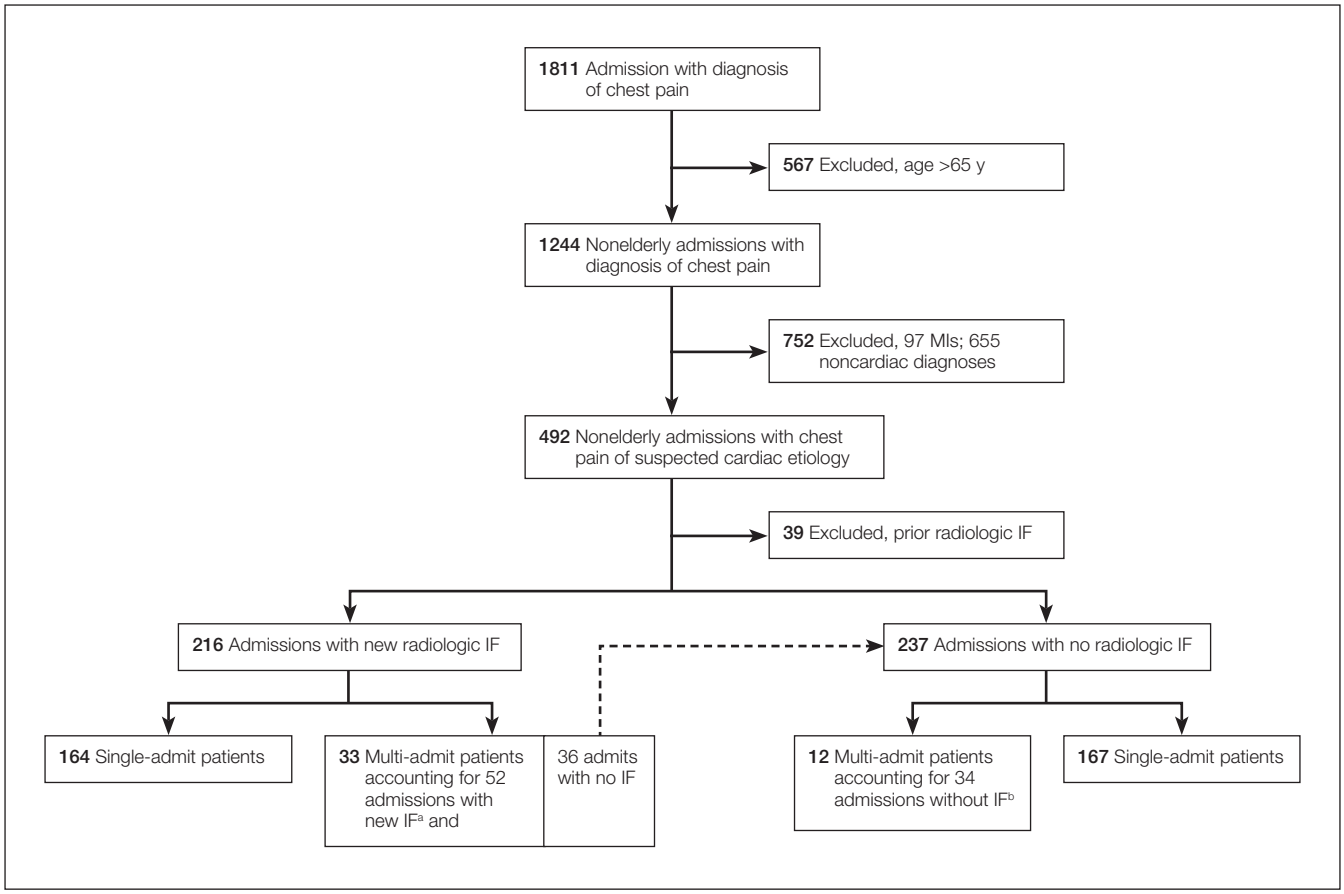

FIG. Flow chart of patient selection.

[a]Patients with multiple admissions and at least 1 admission having radiologic IFs. Only the first admission with new radiologic IFs was included.

[b]Patients with multiple admissions and no radiologic IFs. Only the first admission was included.

NOTE: Abbreviations: IF, incidental findings; MI, myocardial infarction.

the study period. The main focus of CPAC was to look at healthcare disparities and resource utilization in patients with or without a concomitant diagnosis of cocaine use.[12]

Study Population

The Figure shows the selection of the study sample for this analysis. The CPaC Study identified 1811 consecutive admissions for chest pain/angina pectoris (based on admitting diagnosis ICD-9-CM codes: 411.x; 413.x, 414.x; and 786.5x) over 24 months. Per the CPaC Study protocol, patients older than 65 years were excluded (n=567 admissions). After chart review, all admissions diagnosed with acute myocardial infarction (n=97) or noncardiac chest pain (n=655) were excluded. For this analysis, we excluded 39 additional admissions of patients who had known prior radiologic IFs, leading to a sample size of 453 admissions. Three hundred and seventy six patients had accounted for 453 admissions during the study period, and we included1 of these admissions in the analysis using the following process: If a patient had a radiologic IF on any admission during the study period, that patient was included in the "IF" group for the analysis, and data from the first admission with an IF were used for the analysis. If a patient had no radiologic IFs on any admission during the study period, that patient was included in the "no IF" group, and the data from the first admission in the database were used for analysis.

Measurements

Data collection was completed retrospectively by medical record review using a standardized CPaC Study protocol. The database was created and maintained using REDCap (Research Electronic Data Capture; Vanderbilt University, Knoxville, Tennessee) electronic data capture tool hosted at Johns Hopkins University.[13] All data were manually abstracted into REDCap from electronic medical records. All missing values and inconsistent data were reviewed by multiple physicians to ensure data integrity.

We defined all diagnostic (noninterventional; nonlaboratory) testing done during a patient's hospitalization as "diagnostic" tests, except cardiac stress testing and echocardiogram. We defined diagnostic tests as "primary" tests if they were done in response to patients' presenting complaint. We defined diagnostic tests as "secondary" tests if they were done by providers due to IFs. Cardiac computed tomography was included in diagnostic tests. Cardiac testing (echocardiogram, cardiac stress testing, cardiac catheter-

ization and pacemaker placement) was considered separate from the "diagnostic tests" since these were focused cardiac imaging that are interventional in nature with low yield on extra-cardiac radiologic IFs.

Incidental findings were defined as any unexpected findings on diagnostic imaging unrelated to the reason for admission, and were classified based on organ systems and their clinical significance as major, moderate, or minor using a classification previously published by Lumbreras et al.[14] All radiologic IFs data underwent sequential dual review by investigators for accuracy of documentation. Individuals with multiple radiologic IFs belonging to more than one category of clinical significance were categorized with the IFs group of highest clinical significance. Ten percent of the patients with no IFs were reviewed again, and no errors found.

Demographic variables at the time of admission included age, sex, race, level of education, employment status, insurance status, body mass index (BMI), and smoking status. Comorbid conditions at the time of admission consisted of the following: hypertension, diabetes mellitus, chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), history of myocardial infarction, cerebrovascular accident (CVA), congestive heart failure (CHF), drug use and malignancy or history of it. Initial laboratory values were extracted from electronic medical records and included hemoglobin, creatinine, blood urea nitrogen (BUN), aspartate transaminase, alanine transaminase, and alkaline phosphatase. We calculated the estimated glomerular filtration rate (eGFR) using the MDRD (Modification of Diet in Renal Disease) equation.[15] Admission and discharge information as well as whether the patient had a primary care provider, were obtained from medical records. The length of hospital stay was calculated by subtracting date of admission from date of discharge.

Statistical Analysis

We conducted 2 main analyses: 1) a descriptive analysis of the association between patient characteristics (independent variables) and identification of IFs during admission (primary outcome) and 2) an analysis of the association between identification of incidental findings during admission (independent variable) and LOS (primary outcome).

For the descriptive analysis of radiologic IFs, we compared the characteristics of patients with and without radiologic IFs during admission using a t-test (for normally distributed continuous variables) or Mann-Whitney test (for nonnormally distributed continuous variables) and a chi-square or Fisher exact test for categorical variables based on the number of observations. We included variables significantly associated with the occurrence of radiologic IFs ($P < 0.05$) in a multiple logistic regression model to identify characteristics independently associated with presence of radiologic IFs.

Length of stay was right-skewed even after natural logarithm transformation and, therefore, we used negative binomial regression for the analysis of the association between the identification of radiologic IFs during admission and LOS. We included potential confounding variables in the multiple negative binomial regression model based on plausibility of confounding and association with both the exposure (identification of radiologic IFs during admission) and outcome (LOS) at a level of $P < 0.3$. Age, education level, history of drug use, history of CHF, history of CKD, lower eGFR, higher serum creatinine/BUN, hemoglobin, occurrence of cardiac catheterization, stress testing, and multiple admissions during the study period were identified as confounders. For correlated variables (eg, hemoglobin and hematocrit), the variable with the strongest statistical association (lowest P value) was included in the model. In sensitivity analysis, we dropped patients with extreme LOS (longer than 10 days). All analyses were performed using STATA 13 (Stata Statistical Software: Release 13; StataCorp., College Station, Texas).

RESULTS

Table 1 shows the characteristics of the 376 patients included in this study. Overall mean age was 50.5 years, 40% were females, 62% were Caucasian, 66% were unemployed, 84% identified a primary care provider upon admission, and 68% were cared for by a hospitalist. Overall median LOS was 2 days (interquartile range [IQR] = 2). Of the 376 patients in the study, 197 (52%) had new radiologic IFs. Comparing the patients with radiologic IFs and no IFs, it was evident that more radiological tests were performed in the IF group (2.2 tests per patient) in comparison with the no IF group (1.26 tests per patient). Looking at patient characteristics, patients with radiologic IFs were older (52 years vs. 48.8 years; $P < 0.001$), reported a lower education level and lower hemoglobin levels on admission (12.0 gm/dL vs. 13.4 gm/dL; $P = 0.029$), but were more likely to be unemployed (72% vs. 59%; $P = 0.009$), have COPD (19% vs. 10%; $P = 0.007$), and a history of malignancy (7% vs. 2%, $P = 0.04$). In addition, patients in the radiologic IF group had lower rates of cardiac catheterization (18% vs. 28%; $P = 0.02$), were more likely to be readmitted more than once during the study period (17% vs. 7%; $P = 0.02$) and be discharged by hospitalists (75% vs. 60%; $P = 0.003$; Supplemental Table 1).

Overall, 658 diagnostic tests were performed in the study population; of these, 268 (40.7%) tests revealed 364 new radiologic IFs (Supplement Table 2). Of these radiologic IFs, 27 (7.4%) were of major clinical significance, 154 (42%) were of moderate clinical significance, and 183 (50%) were of minor clinical significance (Supplement Table 3). Computed tomography (CT) scans yielded more IFs compared to any other imaging modalities. Of the radiologic IFs of major clinical significance, 3 malignant/premalignant lesions were found. While pulmonary nodules were the most common moderate clinically significant findings, atelectasis and spinal degenerative changes were the most common radiologic IFs of minor clinical significance (Supplement Table 4).

Results of the logistic regression models testing the association between patient characteristics and radiologic IFs are displayed in Table 2. Only age and repeat admissions

TABLE 1. Characteristics of Study Population

Patient Characteristics	Total Study Population, N=376 (%)
Age, y	50.5±9.3
Female	151 (40)
Race	
White	234 (62)
Black	123 (33)
Other (Asian, Hispanic)	19 (5)
Unemployed	248 (66)
Insurance	
Medicare	79 (21)
Medicaid	73 (19)
Private insurance	187 (50)
Self-pay	37 (10)
Education level	
Not completed high school	76 (20)
Completed high school	222 (59)
Completed college	78 (21)
BMI, kg/m^2	31.5±8.1
Hemoglobin level, gm/dL	13.2±1.9
eGFR on admission, mL/min/1.73m^2	81.8±35.4
ALT on admission, units/liter	40.8±40
Tobacco use	
Never smoker	133 (36)
Past smoker	69 (18)
Active smoker	174 (46)
Hypertension	262 (70)
Diabetes mellitus	136 (36)
CKD	66 (18)
Prior MI	82 (22)
COPD	55 (15)
CHF	50 (13)
CVA	46 (12)
Prior diagnosis of malignancy	17 (5)
Drug use	76 (20)
PCP present on admission	317 (84)
Cardiac catheterization during current admission	85 (23)
Stress test during current admission	163 (43)
Echocardiogram during current admission	89 (24)
Discharging provider	
House staff	112 (30)
NP/PA	9 (2)
Hospitalist	255 (68)
LOS (d)[a]	2 (2)
Discharge location	
Home	345 (92)
Other (nursing home, rehabilitation facility, or shelter)	31 (8)
Patients with multiple admissions during study period	45 (12)

[a]Data is median interquartile range.

NOTE: Data displayed as mean± standard deviation for continuous variables, and n (%) for categorical variables.

Abbreviations: ALT, alanine transaminase; BMI, body mass index; CHF, congestive heart failure; CVA, cerebrovascular accident; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; IF, incidental findings; LOS, length of stay; MI, myocardial infarction; NP, nurse practitioner; PA, physician assistant; PCP, primary care provider.

remained significantly associated with radiologic IFs in the fully adjusted model (adjusted odds ratio [OR], 1.04; 95% confidence interval [CI], 1.01-1.06 and 2.68; 95% CI, 1.60-4.44, respectively).

Median LOS was 2 days (IQR=1) for patients with no IFs and 2 days (IQR=2) for patient with radiologic IFs (P = 0.08). Unadjusted negative binomial regression analysis revealed that identification of any radiologic IFs during admission (vs. none) was associated with an increased LOS by 24% (unadjusted IRR, 1.24; 95% CI, 1.06-1.45). After adjustment for confounders, identification of any radiologic IFs during admission remained significantly associated with a longer LOS (adjusted IRR, 1.26; 95% CI, 1.07-1.49). Results remained significant on a sensitivity analysis excluding admissions lasting longer than 10 days (adjusted IRR, 1.21; 95% CI, 1.03-1.42; Supplement Table 5).

Incidental findings of minor and moderate clinical significance were associated with increase in LOS on multiple negative binomial regression (adjusted IRR, 1.27; 95% CI, 1.03-1.57 and 1.24; 95% CI, 1.02-1.52, respectively; Table 3); however, upon dropping length of hospitalization outliers, only radiologic IFs with major clinical significance were associated with increase in length of hospitalization (adjusted IRR, 1.39; 95% CI, 1.04-1.87; Table 3).

Supplemental chart review revealed that 26 patients accounted for the 27 radiologic IFs of major clinical significance. This group had 54% women, median LOS remained 2 days (IQR 2) and, on average, had about 3 diagnostic tests performed per patient. Cardiac testing was performed less on these patients compared to others (Supplement Table S6). Review also revealed that, of the 26 patients, 2 had abnormal labs, 2 had drug abuse/psychiatric issues, and another 2 had radiologic IFs that warranted further consultations, imaging, and longer LOS.

DISCUSSION

Radiologic IFs in patients admitted with chest pain of suspected cardiac origin are a common occurrence as shown in our study. Similar to prior studies, 41% of all radiologic tests done in our study population revealed IFs.[6] The majority of the IFs were of minor to moderate clinical significance and, as reported in the literature, were more common with older age and CT imaging.[14,16] In addition, an IF diagnosed during admission for chest pain was associated with a 26% increase in length of hospital stay.

To our knowledge, we present the first study on the impact of identification of radiologic IFs in hospitalized patients on length of hospital stay and specifically in patients hospitalized with chest pain of suspected cardiac origin. Trends over the past decade have shown a decrease in LOS and hospitalizations but with an increase in health resource utilization.[17,18] Association of radiologic IFs with increase in LOS is significant as this potentially increases hospital-acquired conditions such as infections and resource utilization leading to increase in costs of hospitalizations.[19] This in return is a concern for patient safety.

TABLE 2. Logistic Regression Analysis of Factors Associated with IFs

	Univariate Regression			Multivariate Regression		
Variable	Unadjusted OR	CI	*P* value	Adjusted OR	CI	*P* value
Age (y)	1.04	1.01-1.06	0.001	1.04	1.01-1.06	0.002
Unemployment	0.56	0.36-0.86	0.009	0.88	0.54-1.44	0.626
Education:						
Not completed high school	(1.0) ref			(1.0) ref		
Completed high school	0.61	0.35-1.03	0.06	0.65	0.36-1.18	0.161
Completed college	0.38	0.19-0.73	0.004	0.48	0.23-0.98	0.046
Multiple admissions during study period	2.68	1.64-4.35	<0.001	2.68	1.60-4.44	<0.001
COPD	2.28	1.23-4.20	0.08	1.4	0.71-2.76	0.33
Prior diagnosis of malignancy	3.09	0.99-9.66	0.05	1.66	0.46-6.07	0.435
Cardiac catheterization	0.56	0.34-0.91	0.019	0.65	0.36-1.16	0.146
Hemoglobin level, gm/dL	0.88	0.79-0.99	0.019	0.92	0.82-1.04	0.183
Discharging provider						
House staff	(1.0) ref			(1.0) ref		
NP/PA	0.39	0.08-1.98	0.26	0.32	0.05-1.77	0.192
Hospitalist	1.91	1.22-3.00	0.005	1.62	0.97-2.72	0.065

NOTE: Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; IF, incidental finding; NP, nurse practitioner; OR, odds ratio; PA, physician assistant; ref, referent.

The positive association between LOS and radiologic IFs, interestingly, continued to exist despite sensitivity analysis. Incidental findings of major clinical significance were associated with longer LOS in the sensitivity analysis. Supplemental chart review of patients with major clinical findings suggested more extra-cardiac workup compared to patients with minor/moderate radiologic IFs. This could indicate that the presence of clinically significant radiologic IFs could have led to further inpatient work-up and consultations. The downstream healthcare expenditure associated with workup of IFs in individual radiologic tests is well established.[20] In case of cardiac CT, Goehler et al.[21] found that the healthcare expenditure was high following incidentally detected pulmonary nodules with an overall small reduction in lung cancer mortality. Incidental findings also increase the burden of reporting and concern for medico-legal issues for providers.[4] These concerns are likely valid for hospitalized patients as well.

TABLE 3. Multivariate Negative Binomial Regression of LOS by IF Clinical Significance

Clinical Significance	IRR[a] (LOS)	CI	*P* value
No IF	(1.0) ref		
Minor	1.27	1.03-1.57	0.023
Moderate	1.24	1.02-1.52	0.031
Major	1.33	0.98-1.82	0.071
Drop LOS >10 d			
No IF	(1.0) ref		
Minor	1.16	0.94-1.42	0.15
Moderate	1.20	0.99-1.46	0.057
Major	1.39	1.04-1.87	0.027

[a]Adjusted for age, history of drug abuse, history of congestive heart failure, history of cerebrovascular accident/transient ischemic attack, body mass index, multiple admissions during study period, and cardiac catheterization/cardiac stress test during admission, creatinine, education level, and hemoglobin.

NOTE: Abbreviations: CI, confidence interval; IF, incidental finding; IRR, incident rate ratio; LOS, length of stay; ref, referent.

The socioeconomic trends in the study population were consistent with data from the Bureau of Labor Statistics in that low education is associated with higher unemployment.[22] Although, overall, gender, race and insurance mix were similar in both groups, we did see trends of socioeconomic differences in the patients with radiologic IFs of major clinical significance that might not have been statistically significant owing to the small sample size. Despite the population being relatively of younger age (given our cut off age was 65 years) there was still a positive association with age and presence of radiologic IFs. The higher number of patients with COPD or history of malignancy in the radiologic IF group suggests that an association with IFs could exist for these disease cohorts; however, after adjustment for multiple covariates, such an association did not transpire. Interestingly, patients with no radiologic IFs underwent cardiac catheterization or stress testing more often than patients with discovered IFs. This speaks of 2 possibilities; first, that both tests probably do not yield many extra-cardiac IFs, or, secondly, that these patients did not require further workup. More patients in the IF group had more than 1 admission during the study period, and this was associated with increased odds of detecting radiologic IFs. We hypothesize that this might have occurred because of the diagnostic dilemma in these patients who have multiple admissions for the same reason leading to wider array of diagnostic workup. Indeed, we did not note upon chart review alternative diagnoses in these patients but only more IFs. There are several study limitations to consider. First, the fact that this is a single center study sets limitations to interpretation and generalizability of the data. Second, we cannot exclude the possibility of residual confounding. Third, the small number of patients included in this study precludes definitive identification of more factors potentially associated with IFs. However, this

study sheds light on a yet unidentified problem within the realm of inpatient management especially for the internists and hospitalists. We tried to limit bias to the extent possible by including only 1 presenting complaint and age-restricting the population.

CONCLUSION

Incidental findings are both clinical and financial challenges to the medical field. This study attempted to shed light on impact of radiologic IFs on care and resource utilization in patients admitted with chest pain of suspected cardiac origin. The positive association between radiologic IFs and length of hospital stay implies that the presence of IFs is associated with increase in LOS and indirectly a likely increase in overall healthcare expenditure. Given the high incidence of radiologic IFs, assuming that these will be present on radiologic tests, should be more a norm than an exception. Providers should know that radiologic testing, especially CT, is associated with detection of IFs.[16] By avoiding inappropriate ordering of imaging, the issue of IFs could be mitigated.

While radiologists have recommendations about necessary follow-up for some IFs,[7] no clear follow-up guidelines exist for most IFs arising in hospitalized patients. Further prospective and cost analysis studies are needed to assess the overall impact of IFs on other hospitalized patient populations and on the healthcare system in general.

Disclosure: The authors report no conflicts of interest.

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Overuse of Troponin? A Comprehensive Evaluation of Testing in a Large Hospital System

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Troponin assays are integral to the diagnosis of acute myocardial infarction (AMI), but there is concern that testing is over utilized and may not conform to published guidelines. We reviewed all testing performed at 14 hospitals over 12 months and associated troponin values with the primary and secondary diagnoses for each visit. Troponin was determined to be negative, indeterminate or elevated based on reference ranges. The majority of troponin measurements were single, not serial (64%). The rate of AMI was low, with only 3.5% of tested patients having a primary or secondary diagnosis of AMI. Sensitivity, specificity and negative predictive value were excellent, exceeding 90%. However, positive predictive value was low, suggesting testing of populations with diseases known to be associated with elevated troponin levels in the absence of AMI. The majority (79%) of elevated troponin values were associated with primary diagnoses other than AMI. Only 28% of elevated troponins were associated with a primary or secondary diagnosis of AMI. These data suggest possible overuse of troponin testing in our healthcare system. *Journal of Hospital Medicine* 2017;12:329-331. © 2017 Society of Hospital Medicine

The ability of serum troponin measurement in the diagnosis of acute myocardial infarction (AMI) was validated in patients with at least a moderate pretest probability for the disease.[1] The diagnostic yield of troponin testing in clinical trials has been between 20% and 50%, excluded patients thought unlikely to have AMI. In practice, physicians often encounter low-risk patients and patients in whom the diagnosis on initial presentation is unclear. Several noncardiac diagnoses, such as pneumonia and respiratory failure, are associated with an elevated troponin level in the absence of AMI, but patients can present with symptoms similar or identical to those of patients who present with AMI.[2-4] Elevated troponin level in sepsis has been associated with worsened prognosis, though there is no evidence that this finding alters management. An American College of Cardiology Foundation opinion published in 2012 expressly recommends against troponin testing in patients with sepsis.[4]

The only guideline-based indication for troponin testing is the diagnosis or exclusion of AMI.[5] We conducted a comprehensive review of troponin testing in our healthcare system to see whether testing might be used in clinical settings in which AMI was unlikely.

METHODS

We retrospectively obtained data on all visits to 14 hospitals in an integrated healthcare system in Texas between June 2013 and June 2014. We analyzed data for all hospital encounters during which a troponin assay was ordered and a troponin level reported—including qualitative point-of-care assays and quantitative laboratory troponin I measurements. We identified 93,436 visits. Quantitative measurements were divided into negative (<0.05 ng/mL), indeterminate (0.05-0.09 ng/mL), and elevated (>0.09 ng/mL), based on the reference ranges reported to physicians. We associated troponin levels with *ICD-9* (*International Classification of Diseases, Ninth Revision*) primary and secondary diagnoses, grouping *ICD-9* codes 410 (AMI), 411 (other acute or subacute forms of ischemic heart disease [IHD]), 412 (old myocardial infarction), 413 (angina pectoris), and 414 (other forms of chronic IHD) as representing IHD diagnoses.

To further evaluate troponin testing, we constructed 2 contingency matrices (Table).[6] We included visits for which both primary and secondary diagnoses were available for review and for which quantitative troponin I measurements were available; 92,445 encounters met criteria for inclusion in matrix calculations. In the first matrix (part A of Table), a primary diagnosis of any AMI (*ICD-9* code 410) was used as "positive" and all others "negative." In the second matrix (part B of Table), "positive" includes any primary or secondary diagnosis of AMI.

RESULTS

We identified a total of 93,436 hospital visits associated with troponin testing; 179,239 troponin measurements were associated with these visits (an average of 1.81 per encounter). Of these visits, 59,897 (64.1%) were associated with a single measurement. Of the 179,239 measurements, 147,051 (82.1%) were negative, 21,881 (12.1%) indeterminate, and 10,307 (5.8%) positive. Primary diagnoses of hypertension,

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Received: May 12, 2016; **Revised:** September 11, 2016; **Accepted:** October 17, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2732

TABLE. Contingency Matrices Evaluating Elevated Troponin Levels and AMI Diagnoses[a]

A. Primary Diagnosis of AMI	AMI	No AMI	Total	
Troponin level, ≥0.1 ng/mL	2238	8069	10,307	
Troponin level, <0.1 ng/mL	167	81,971	82,138	
Total	2405	90,040	92,445	
B. Primary or Secondary Diagnosis of AMI	**AMI**	**No AMI**	**Total**	
Troponin level, ≥0.1 ng/mL	2969	7338	10,307	
Troponin level, <0.1 ng/mL	294	81,844	82,138	
Total	3263	89,182	92,445	
C. Primary vs Any Diagnosis of AMI	**Primary**	**95% CI**	**Any**	**95% CI**
Prevalence	0.026	0.025-0.027	0.035	0.034-0.037
Sensitivity	0.931	0.920-0.940	0.910	0.900-0.920
Specificity	0.910	0.909-0.912	0.918	0.916-0.920
Positive predictive value	0.217	0.209-0.225	0.288	0.279-0.297
Negative predictive value	0.998	0.998-0.998	0.996	0.996-0.997

[a]Elevated troponin levels (≥0.1 ng/mL) were associated with either (A) primary diagnoses of AMI or (B) all primary or secondary diagnoses of AMI. (C) Disease prevalence, sensitivity, specificity, and positive and negative predictive values were calculated for each condition; CIs were calculated using the log method.[11]

NOTE: Abbreviations: AMI, acute myocardial infarction; CI, confidence interval.

dizziness, abdominal pain, anxiety, dehydration, and headache associated with troponin testing comprised 6127 encounters and had no associated elevated troponin levels. Several non-cardiac primary diagnoses were associated with significant numbers of elevated troponin values including septicemia (27%), acute respiratory failure (28%), and cerebrovascular accident (10%). Seventy-six percent of encounters associated with troponin testing had no primary or secondary IHD diagnosis. Only 2% of 16,941 visits with a primary diagnosis of chest pain were associated with abnormal troponin levels (Figure).

Analysis of contingency matrices revealed AMI prevalence of 2.6% when primary AMI diagnoses were considered and 3.5% when any AMI diagnoses were considered. Sensitivity and specificity were high (>90%), and negative predictive value extremely high (>99%) in each circumstance. However, positive predictive values were low (21.7% and 28.8%, respectively), indicating the majority of patients with elevated troponin levels were not reported to have AMI by attending physicians.

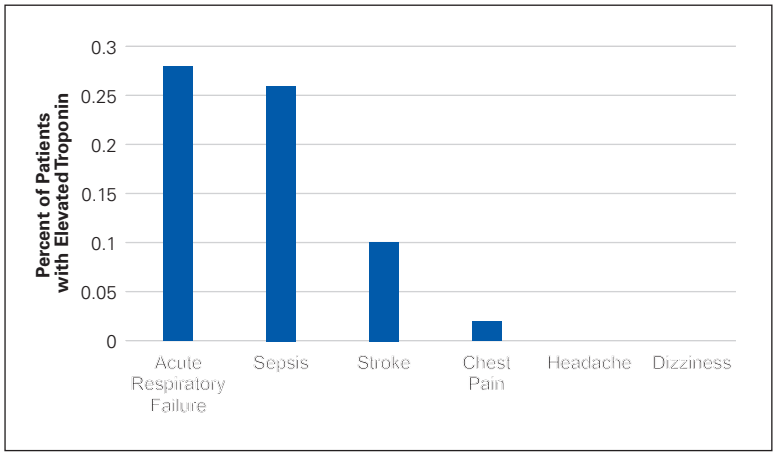

FIG. Notable non-AMI primary diagnoses associated with elevated troponin I values. A selection of primary diagnoses other than AMI is presented with the corresponding percentage of elevated (≥0.1 ng/ml) troponin I measurements (0.00-1.00). For comparison, the percentage of elevated troponin I measurements associated with a primary diagnosis of AMI was 0.93.

NOTE: Abbreviation: AMI, acute myocardial infarction.

DISCUSSION

We were surprised to find that troponin level was measured only once during 64% of the hospital encounters. Although there are clinical scenarios in which a single measurement might be indicated, detecting a rise or fall in troponin level is integral to the diagnosis of AMI, which is why guidelines recommend serial measurement.[4] We were also surprised to find a low rate of either primary or secondary AMI in patients tested. As others have found,[2,3] elevated troponin levels were associated with noncardiac primary diagnoses, such as sepsis, respiratory failure, and stroke. Of interest, the majority (72%) of patients with elevated troponin levels did not receive a primary or secondary diagnosis of AMI.

Determining the appropriate level of use for a diagnostic laboratory test can be difficult. Primary diagnostic codes, including codes for headache and dizziness, accounted for thousands of tested patients but were associated with no elevated troponin levels. On the other hand, sepsis, pneumonia, and stroke were associated with high rates of elevated troponin levels. Elevated troponin levels likely precipitate cardiology consultation and testing, which increase cost of care perhaps without improving either quality or value of care. Howev-

er, evidence for the potential prognostic value of testing has led to ongoing research at our institution to evaluate whether troponin measurement might guide better management of such patients.

Appropriate use criteria have been developed for many diagnostic studies, including echocardiography, stress testing, and cardiac catheterization, but not for laboratory testing. Our data suggest possible overuse of troponin testing in our healthcare system. The low AMI incidence we found (2.6%-3.5%) indicates that many patients without AMI are being tested.

Although it is impossible to accurately estimate sensitivity and specificity of testing post hoc, it is reassuring to see that measured sensitivity, specificity, and negative predictive values were all high and consistent with published values from prospective clinical trials.[7,8]

As potential roles for troponin testing develop for patients without primary cardiac disease, it becomes even more important to develop guidelines for testing and to avoid universal testing of all hospitalized patients. The high negative predictive value of troponin testing (99%) is attractive to physicians who want to avoid missing AMI. Electronic order sets allow troponin testing to be included alongside "standard" testing, such as complete blood cell counts and comprehensive metabolic panels, and may contribute to overuse.

The troponin assays used in our healthcare system in 2014 likely will be replaced with high-sensitivity assays currently being used in Europe.[9,10] These high-sensitivity assays can improve sensitivity but cannot be expected to increase positive predictive value or reduce false detection rates. When performed as single measurements, hs troponin has the potential to increase the number of elevated troponins detected that are not associated with AMI.

On the basis of our data, we have initiated a system-wide program to improve performance of troponin testing in our healthcare system. We are working with hospitalists and critical care and emergency department physicians to ensure that serial measurements are being performed and that the correct patients are being tested. Future data collection will help determine the success or failure of these efforts.

Disclosure: Nothing to report.

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It All Just Clicks: Development of an Inpatient E-Consult Program

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Although the use of electronic consultations (e-consults) in the outpatient setting is commonplace, there is little evidence of their use in the inpatient setting. Often, the only choice hospitalists have is between requesting a time-consuming in-person consultation or requesting an informal, undocumented "curbside" consultation. For a new, remote hospital in our healthcare system, we developed an e-consult protocol that can be used to address simple consultation questions. In the first year of the program, 143 e-consults occurred; the top 5 consultants were infectious disease, hematology, endocrinology, nephrology, and cardiology. Over the first 4 months, no safety issues were identified in chart review audits; to date, no safety issues have been identified through the hospital's incident reporting system. In surveys, hospitalists were universally pleased with the quality of e-consult recommendations, though only 43% of consultants agreed. With appropriate care for patient selection, e-consults can be used to safely and efficiently provide subspecialty expertise to a remote inpatient site. *Journal of Hospital Medicine* 2017;12:332-334. © 2017 Society of Hospital Medicine

Electronic consultation (e-consult) in the outpatient setting allows subspecialists to provide assessment and recommendations for patients without in-person visits.[1] An e-consult is an asynchronous communication that uses the electronic medical record (EMR) and typically involves an electronic order from a requesting provider and an electronic note from a consulting provider. The initial motivation for developing this consultation modality was to improve access to subspecialty care for patients in the primary care setting, and findings of studies at several sites support this claim.[1-4] In addition, e-consult may also reduce cost because converting unnecessary face-to-face encounters into e-consults reduces patients' travel costs and healthcare organizations' expensive subspecialty clinic time.[3,5] Moreover, instead of addressing less complex clinical questions in informal, undocumented face-to-face or telephone "curbside" consultations with specialists, providers can instead ask for e-consults and thereby ensure thorough chart review and proper documentation.[6]

Use of e-consults in the inpatient setting is relatively novel.[7] In addition to having the advantages already mentioned, e-consults are faster than in-person bedside consultations and may be beneficial in the fast-moving inpatient care setting. Finally, healthcare systems with multiple hospital sites may not have the capacity to physically locate subspecialists at each site, which makes e-consults attractive for avoiding unnecessary travel time.

In this article, we describe how we developed an inpatient e-consult protocol for a new, remote hospital within our healthcare system and explore data on safety and physician attitudes after e-consult implementation.

METHODS

The Institutional Review Board of the University of California San Francisco (UCSF) approved this study.

Setting

In February 2015, UCSF opened a new hospital in the Mission Bay neighborhood of San Francisco, 4 miles from the existing hospital. The new hospital is home to several adult inpatient services: urology, otolaryngology, colorectal surgery, obstetrics, and gynecologic surgery. A hospitalist is on-site 24 hours a day to provide consultation for these services around issues that relate to internal medicine. A hospitalist who requires subspecialty expertise to answer a clinical question can request a consultation by in-person visit, video telemedicine, or e-consult, each of which is available 24/7. Almost all of the medicine subspecialists work on the existing campus, not in Mission Bay.

Protocol Development and Implementation

The protocol for the e-consult program was developed over several months by an interdisciplinary group that included 3 hospitalists, 1 obstetrician, 1 project manager, and 1 informaticist. The group outlined the process for requesting and completing an e-consult (Figure), designed a note template for consultants to use for EMR documentation, conducted outreach with subspecialty groups to discuss the protocol, and developed an EMR report to track e-consult use and content over time. As our medical center does not bill payers for inpatient e-consults, e-consult note tracking is used to provide reimbursement internally, from the medical center to the respective departments of the consultants. Reim-

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Received: August 11, 2016; **Revised:** October 22, 2016; **Accepted:** November 9, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2740

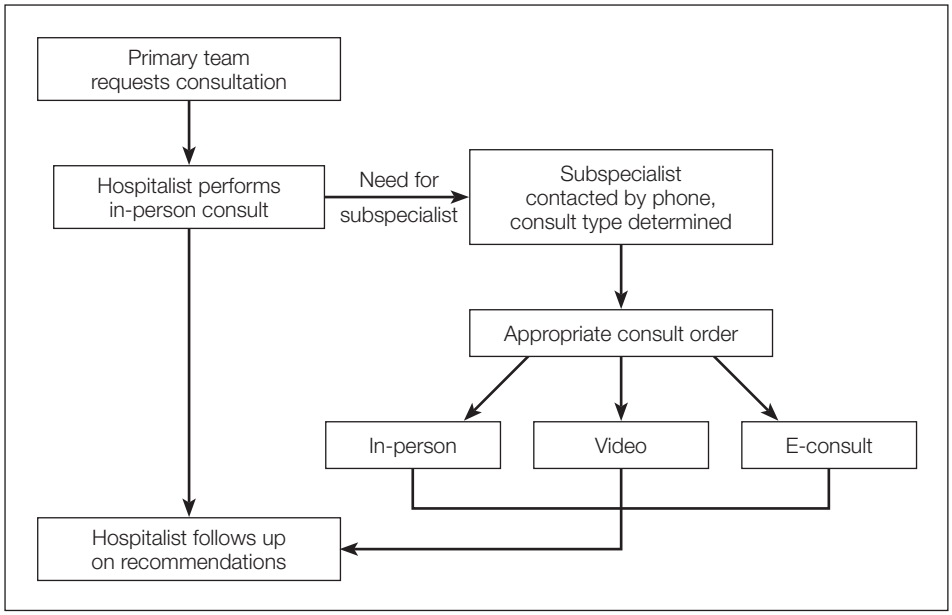

FIG. Process for requesting and completing an e-consult. Order not mandatory.

bursement is made at a set rate per e-consult note, with the rate set to approximate the reimbursement of a low-acuity in-person consult on the main campus.

The workflow of an e-consult is as follows: (1) When a primary team requires a consultation on an issue that falls within the purview of internal medicine, it pages the on-site hospitalist. (2) The hospitalist accepts the consultation by phone, reviews the chart, and examines the patient. (3) If the hospitalist requires subspecialty assistance to answer a clinical question, he or she contacts the appropriate subspecialty service by pager. (4) The subspecialist speaks with the hospitalist about the consultation question, and together they decide if an e-consult is appropriate, based on the complexity of the clinical scenario. (5) The subspecialist reviews the patient's chart and documents their care plan recommendations in an e-consult note. Consultants can use e-consult for both initial and follow-up assessment, and there is no strict requirement that they also contact the hospitalist or the primary team by phone in addition to consultation note. Given their novelty, almost all e-consults are performed by subspecialist attendings, not residents or fellows.

Evaluation

Each month, we tracked e-consult use using an EMR report built as part of the implementation of the program. For the first four months of implementation, every patient who received an e-consult also had a manual chart review of the period around the e-consult, performed by a hospitalist, in order to audit for any potential safety issues. These issues included, for example, an e-consult performed for a patient whose complexity or severity of illness was felt to be too great to defer an in-person visit, or a patient who received e-consult recommendations that were significantly retracted in a follow-up in-person note.

Eight months after the program started, we assessed experience by electronically surveying the 9 hospitalists and 11 consultants who had requested or performed at least 2 e-consults.[8] Survey items were measured on a 5-point Likert scale: *strongly disagree* to *strongly agree*. The items, which related to ease of calling for a consultation, quality of e-consults, impact on clinical care, safety concerns, and satisfaction, were inspired by themes identified in a systematic review of the literature on e-consults in the outpatient setting.[2] We sent 2 reminders to responders. Data were summarized using descriptive statistics. Analysis was performed in SPSS version 22.0 (IBM).

RESULTS

There were 143 initial subspecialty consultations by e-consult between program launch in February 2015 and manuscript preparation in February 2016, an average of 11 e-consults per month. There were 313 total e-consult notes (these included both initial and follow-up e-consult notes). By comparison, 240 initial in-person consultations occurred during the same period, and there were 435 total in-person consultation notes (46% new or initial notes, 54% follow-up notes). The top 5 subspecialties by volume of e-consults were infectious disease (35%), hematology (20%), endocrinology (14%), nephrology (13%), and cardiology (8%). For reference, e-consults are also available from psychiatry, neurology, oncology, gastroenterology, pulmonology, and rheumatology. Percentage of consultations performed during daytime hours (defined as 8 a.m. to 5 p.m.) was 92% for e-consults and 96% for in-person consultations.

There were no e-consult–related patient safety issues reported through the medical center's incident reporting system during the study period. There were also no patient safety issues identified in the manual audits of 80 charts during the first 4 months of the program.

Seven (78%) of 9 hospitalists and 7 (64%) of 11 consultants completed the survey. Both groups agreed that e-consults were easy to use and efficient (Table). All hospitalists were satisfied with the quality of e-consult recommendations, but only 3 (43%) of the 7 consultants agreed they could provide high-quality consultation by e-consult. In their comments, 2 consultants expressed concerns. One concern was about missing crucial information by performing only a chart review, and the other was about being tempted to perform an e-consult simply because it is expedient.

DISCUSSION

Although use of e-consults in the outpatient setting is relatively commonplace, our program represents a novel use

TABLE. Results of E-Consult Survey Given to Hospitalists and Consultants

Hospitalists (n = 7)	Agree or Strongly Agree, n (%)	Consultants (n = 7)	Agree or Strongly Agree, n (%)
It is easy to request an e-consult	5 (71)	It is easy to provide an e-consult	4 (57)
I am satisfied with the quality of e-consult recommendations	7 (100)	The referring provider adequately communicates the e-consult question and important clinical information	5 (71)
It is *less* safe to accept recommendations from an e-consult than in an in-person consult	1 (14)	It is *less* safe to provide recommendations through an e-consult than in an in-person consult	2 (29)
I am satisfied with the turnaround time for e-consults	6 (86)	I can provide a high-quality consultation through e-consult	3 (43)
An e-consult usually eliminates the need for an in-person consult	5 (71)	It is more efficient for me to perform an e-consult than an in-person consult	6 (86)
Recommendations from an e-consult often modify my care plan	6 (86)	The e-consult program should be expanded to other sites at my institution	3 (43)
Overall I am satisfied with the e-consult program	6 (86)		

of e-consults in safely and efficiently providing subspecialty consultation to inpatients at a remote hospital.

For hospitalists, an e-consult system offers numerous benefits. Clinical questions beyond an internists' scope of practice come up often, and simple questions might traditionally result in an informal curbside consult. While a curbside consult provides answers faster than an in-person visit, it creates risks for the requesting hospitalists: the consultants only know what they are told, whether the information is incomplete or erroneous; their opinions are given without documentation or compensation, which reduces a sense of accountability; and the lack of documentation does not allow their advice to persist in the chart as a reference for future providers.[9] Our e-consult program solves these problems by requiring that consultants perform chart review and provide documentation as well as obligating the medical center to pay a small compensation to consultants for their time. We hope this lowers the bar to requesting consultation for remote sites, where the alternative would be burdensome travel time to do an in-person visit.

In our study, hospitalists were universally pleased with the quality of e-consult recommendations, but only 43% of consultants agreed. These findings correlate with the literature on e-consults in the outpatient setting.[2] Unfortunately, our survey comments did not shed further light on this sentiment. In the outpatient literature, consultants were most concerned with having a clear clinical question, facing the liability of providing recommendations without performing an examination, and receiving appropriate compensation for answering e-consults.

The generalizability of our program findings is limited most significantly by the particular arrangement of our clinical services: Our remote site is home to a select group of adult inpatient services, a hospitalist is available on-site for these services 24 hours a day, and the distance to the remote site can be overcome with modest effort should a patient require an in-person visit in the initial or follow-up period. The generalizability of our safety findings is limited by the use of a single reviewer for chart auditing.

Given the rise of accountable care organizations and the prevalence of hospital mergers in the healthcare landscape, we believe that healthcare systems that operate remote sites under constrained budgets could look to e-consults to more cost-effectively extend subspecialty expertise across the inpatient enterprise. With improvements in health information exchange, it may also become feasible for consultants to offer e-consults to hospitals outside a medical center's network. Our study showed that inpatient e-consult programs can be developed and implemented, that they appear not to pose any significant safety issues, and that they can facilitate delivery of timely clinical care.

Acknowledgment

The authors thank Raphaela Levy-Moore for creating and implementing the e-consult note template for our electronic medical record.

Disclosure: Nothing to report.

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Clinical Utility of Routine CBC Testing in Patients with Community-Acquired Pneumonia

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The goal of this study was to identify situations in which routine complete blood count (CBC) testing could be avoided in patients with community-acquired pneumonia (CAP). This was a retrospective study of 50 patients with CAP. Vital signs, lab results, assessment and plan data, and computerized provider order entry logs were collected to determine if a lab result or clinical finding changed clinical management. Clinical stability was defined based on Patient Outcomes Research Team study criteria. There were 94 CBCs obtained after admission, of which only 6 were associated with management changes. Only two of these instances involved management changes related to patients' pneumonia, while the other cases represented chronic illnesses. Among all patients, the positive likelihood ratio of a post-admission CBC predicting a change in clinical management was low (1.12 [95% confidence interval, 0.86-1.44]). Low utility of CBC testing after admission may represent an opportunity to improve the value of care in CAP patients. *Journal of Hospital Medicine* 2017;12:336-338. © 2017 Society of Hospital Medicine

Avoiding repeated complete blood count (CBC) tests in the face of clinical and lab stability is a focus of the Choosing Wisely® initiatives launched by the American Board of Internal Medicine Foundation[1] and endorsed by the Society of Hospital Medicine.[2] However, specific scenarios in which daily morning labs can be safely avoided have not been identified. The goal of this study was to identify situations in which routine CBC testing can be avoided in patients with community-acquired pneumonia (CAP), one of the most common reasons for hospital admission.[3]

METHODS

This was a retrospective study of 50 patients with CAP discharged from our hospital between February 1, 2015 and May 1, 2015. We performed chart abstractions collecting daily vital signs, lab results, provider notes including assessments and plans (A&Ps), and order entry logs, as well as documentation indicating whether a lab result or clinical finding appeared to affect clinical management (eg, a new order or documentation of changing plans). Both escalations and de-escalations were included as management changes. For example, if the note stated "Persistent leukocytosis, add vancomycin," then the clinical action of expanded antibiotic coverage would be attributed to the CBC.

We defined clinical stability based on Definition B of the Pneumonia Patient Outcomes Research Team (PORT) study criteria.[4] We used descriptive statistics and likelihood ratios to characterize the utility of CBC testing in terms of producing clinical management changes. Likelihood ratios were calculated with the "test" representing a CBC being ordered or not ordered and the outcome being any change in management independent of whether it was due to the CBC.

RESULTS

Of 50 patients, 33 (66%) were female, the mean age was 75 years, the mean length of stay was 2.8 days, and the median CURB-65 score,[5] an estimate of mortality in CAP used for decision-making about inpatient versus outpatient treatment, was 1 (25^{th} to 75^{th} interquartile range: 1, 2); no patients had a CURB score greater than 3 (Table 1). Forty-one (82%) patients met PORT clinical stability criteria prior to discharge, and 30 (75% of stable patients) had CBCs obtained.

On days after admission, 94 subsequent CBCs were obtained. Of these CBCs, 6 (6.4%) were associated with management changes indicated in documentation or orders (Table 2). In 2 of the 6 patients, management changes were likely relevant to pneumonia. In the first case, the patient had a white blood cell count (WBC) of 15.4 on the planned day of discharge but no accompanying clinical changes. Her discharge was potentially delayed pending a repeat CBC which again showed a WBC 14.7; the patient was then discharged without any additional changes in plan. In the second case, the patient experienced new-onset altered mental status on hospital day 3 and increasing O_2 requirement with a rising WBC noted on hospital day 4. Repeat chest x-ray, repeat blood cultures, and an ultrasound for parapneumonic effusion were obtained, and the patient's symptoms and signs resolved over a period of days without changes in treatment. In the 4 other cases, available documentation suggested

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Received: May 31, 2016; **Revised**: October 14, 2016; **Accepted**: November 19, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2734

the hemoglobin abnormalities found represented chronic or incidental illnesses, specifically iron deficiency anemia, iatrogenic anemia due to fluid resuscitation and hemodilution, previously known chronic lymphocytic leukemia, and thrombocytopenia due to acute infection. In all 6 instances, CBC values improved without treatment intervention.

Among all patients, the positive likelihood ratio of CBCs obtained after admission in terms of being followed by a change in clinical management was very poor (1.12, 95% confidence interval [CI], 0.86-1.44). For clinically unstable patients, there were 64 CBCs ordered, and the likelihood ratio was similar at 0.98 (95% CI, 0.75-1.29). The positive likelihood ratio among clinically stable patients, who had 30 CBCs ordered, was still quite weak, though confidence intervals were wider (1.23, 95% CI, 0.66-2.29).

TABLE 1. Patient Characteristics

Characteristic	n (%)
Age, mean	75.2 y
Race	
White	21 (42)
Black	4 (8)
Hispanic, Asian, other	25 (50)
Length of stay	2.8 days
Smoking status	
Current	4 (8)
Former	18 (36)
Never	28 (56)
Comorbid conditions	
COPD	12 (24)
Asthma	7 (14)
CHF	5 (10)
CKD	7 (14)
CURB-65 score	
0	8 (16)
1	19 (38)
2	21 (42)
3	3 (6)
4 or 5	0 (0)

NOTE: Abbreviations: CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

DISCUSSION

Though small, our initial study suggests the potential opportunity for savings if Choosing Wisely® recommendations for CBC testing were implemented in patients with community-acquired pneumonia.

Our study has several limitations. Note-writing practices and ordering patterns likely varied between providers, and documentation bias may play a role in our results. However, we defined whether a CBC was associated with changes in clinical decision-making or management by incorporating a number of mutually reinforcing elements of the medical record. We recognize, however, that our approach may not capture undocumented clinical issues or other cognitive (eg, reassurance of clinical resolution) reasons why CBCs were obtained.

Even with these limitations, the likelihood of a CBC value meaningfully changing clinical management among patients with CAP appears to be quite low as evidenced by the case descriptions, particularly when obtained in stable patients by PORT criteria and on the day of discharge. Whether clinical stability as measured by PORT score can be used to target patients in whom CBC testing is unnecessary is difficult to discern from our data, as the overall

TABLE 2. Complete Blood Counts and Changes in Management

Day	Initial Evaluation (Emergency Room and First Admitting Team Note)	All Days of Hospitalization (Excluding Admission Day)	Day of Discharge
Patients with CBCs ordered (n, %)	50 (100)	94 (N/A)[a]	26 (52)
CBCs with any abnormal value (n, %)	41 (82)	87 (93)	25 (96)
CBCs with any mention in note (n, %)	30 (60)	32 (34)	11 (42)
CBCs with any associated management changes (not restricted to pneumonia) (n, %)	6 (12)	6 (6.4)	2 (7.7)
Patients meeting clinical stability criteria[b] (n, %)	9 (18)	54 (N/A)[c]	41 (82)
Patients meeting clinical stability criteria and who had clinical management changes due to CBC results (n, %)	3 (33)	2 (6.7)	2 (10)
Patients not meeting clinical stability criteria and who had clinical management changes due to CBC results (n, %)[d]	3 (7.3)	4 (6.3)	0 (0)

[a]Represents total number of CBCs ordered.

[b]Clinical stability criteria are based on vital signs cutoffs for clinical stability as defined by Definition B of the PORT study.

[c]Represents total number of inpatient days that patients met vital stability criteria.

[d]Denominator n = 41 for initial evaluation; n = 64 for all days of hospitalization; n = 6 for discharge.

NOTE: Abbreviation: CBC, complete blood count.

utility of CBCs obtained after admission was quite low and the rate of changes in management was also low. However, even if CBCs are not particularly costly, unnecessary testing may produce harm in the form of prolonged length of stay, making even one unnecessary CBC potentially extremely expensive. More research involving larger-scale studies are needed to determine the "number needed to screen" for the daily CBC in CAP to determine if the cost savings from overtesting and treatment outweigh the potential benefit of a single CBC that changes management.

Disclosure: Nothing to report.

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Planning and Designing the Improving Addiction Care Team (IMPACT) for Hospitalized Adults with Substance Use Disorder

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People with substance use disorders (SUD) have high rates of hospitalization and readmission, long lengths of stay, and skyrocketing healthcare costs. Yet, models for improving care are extremely limited. We performed a needs assessment and then convened academic and community partners, including a hospital, community SUD organizations, and Medicaid accountable care organizations, to design a care model for medically complex hospitalized patients with SUD. Needs assessment showed that 58% to 67% of participants who reported active substance use said they were interested in cutting back or quitting. Many reported interest in medication for addiction treatment (MAT). Participants had high rates of costly readmissions and longer than expected length of stay. Community stakeholders identified long wait times and lack of resources for medically complex patients as key barriers. We developed the Improving Addiction Care Team (IMPACT), which includes an inpatient addiction medicine consultation service, rapid-access pathways to posthospital SUD treatment, and a medically enhanced residential care model that integrates antibiotic infusion and residential addiction care. We developed a business case and secured funding from Medicaid and hospital payers. IMPACT provides one pathway for hospitals, payers, and communities to collaboratively address the SUD epidemic. *Journal of Hospital Medicine* 2017;12:339-342. © 2017 Society of Hospital Medicine

Addiction is a national epidemic that represents both a pressing need and a significant burden to the healthcare system.[1] Hospitals are increasingly filled with people admitted for medical complications of substance use disorders (SUD).[2] People with SUD have longer lengths of stay (LOS) and high readmission rates.[3] Hospitalization often does not address the root cause—the SUD. For example, many hospitals replace heart valves and deliver prolonged courses of intravenous (IV) antibiotics for endocarditis from injection drug use but do not offer addiction medicine consultation, medication for addiction treatment (MAT), or linkage to posthospital SUD treatment.[4,5]

Hospitalization can provide reachable moments for initiating addiction care.[6] Medications for opioid[7] and alcohol use disorders[8] can be started during hospitalization, promoting engagement in outpatient SUD care[7] and increased uptake of MAT,[7-9] and reducing readmissions.[8,10] Yet, medications for SUD are underprescribed,[11,12] and most hospitals lack inpatient addiction medicine services and pathways to timely SUD care after discharge. Furthermore, traditional SUD treatment programs are often not equipped to manage medically complex patients or they have long waitlists.[13] Most behavioral-physical health integration occurs in ambulatory settings. This fails to engage patients who do not access primary care. There is an urgent need for models that can improve care for hospitalized patients with SUD.

Here, we describe our experience using patient needs assessment to engage stakeholders and drive local systems change. We also describe the resulting care model, the Improving Addiction Care Team (IMPACT). Our experience provides a potentially useful example to other hospitals and communities seeking to address the national SUD epidemic.

METHODS

Setting

In 2012, Oregon transformed its Medicaid system by establishing 16 regional "coordinated care organizations" (CCOs) to improve outcomes and slow healthcare spending.[14] In a CCO environment, hospitals assume increased financial risk, yet reforms have focused on the outpatient setting. Therefore, executive leadership at Oregon Health & Science University (OHSU), an urban academic medical center, asked clinician-leaders to design point-of-care improvements for Medicaid-funded adults and build on existing models to improve care for socioeconomically vulnerable adults.[15,16] One priority that emerged was to make improvements for hospitalized adults with SUD. Of the adult inpatients at OHSU, 30% have Medicaid and 15% have SUD by administrative data alone. Before we started our work, OHSU lacked inpatient addiction medicine services.

Local Needs Assessment

To understand local needs and opportunities, we surveyed hospitalized adults with SUD. We used the electronic health

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Received: September 25, 2016; **Revised:** February 8, 2017; **Accepted:** February 16, 2017

2017 Society of Hospital Medicine DOI 10.12788/jhm.2736

record to generate a list of inpatients flagged by nurses for risky alcohol or drug use. A research assistant screened consecutive adults (≥18 years old) and invited those who screened positive for alcohol use (Alcohol Use Disorders Identification Test–Consumption [AUDIT-C])[17] or drug use (single-item screener)[18] to participate. We excluded non-English speakers, incarcerated adults, people using only marijuana or tobacco, psychiatry inpatients, and people unable to consent. Surveys assessed social and demographic factors, healthcare utilization, substance use severity, and treatment experience. Participants who reported high-risk illicit drug or alcohol use[19] were asked to indicate their readiness to change on a 3-point scale developed for this study. Response range included: *no interest, interest in cutting back,* or *interest in quitting*. A subset of participants completed in-depth qualitative interviews exploring patient perceptions of substance use treatment needs.[20] We obtained hospital administrative data from hospital financial services.

Partner Engagement

We identified community partners with which we had an individual or organizational relationship and a common interest and potential for collaboration. All invited partners agreed to attend initial meetings. We convened leadership and frontline staff across partners. OHSU staff included hospital nursing and social work leaders; infectious disease, hospitalist, and addiction physicians; and health services researchers. Community organizations included Central City Concern (CCC), a community organization serving people facing homelessness and addiction; CODA, Inc., a nonprofit SUD treatment agency; and Coram/CVS infusion pharmacy.

Collectively, we reviewed needs assessment findings and examples from the literature[7-9] to develop strategies to address patient and system needs. We used patient narratives to foster alignment and prioritized areas in which integration could improve quality and costs. We assumed we would petition OHSU and/or Medicaid CCOs to finance efforts and saved potentially challenging budget discussions for later, when partnerships would be more developed. Our task force attended more than 3 large-group meetings and numerous small-group meetings to develop IMPACT.

RESULTS

Needs Assessment

Between September 2014 and April 2015, a research assistant approached 326 patients. Of these, 235 (72%) met study inclusion criteria, and 185 (78%) agreed to participate (Table 1). Of people who reported any substance use within the preceding 3 months, 58% of alcohol users and 67% of drug users said they were interested in cutting back or quitting. Fifty-four percent of participants with moderate- to high-risk opioid use and 16% with moderate- to high-risk alcohol use reported strong interest in MAT. In qualitative interviews, participants described inadequately treated withdrawal, the importance of trust and choice, and long wait times as a barriers to entering treatment after hospital discharge.[20]

Administrative data revealed high rates of hospital readmissions and longer than expected LOS (Figure). Mean LOS was 10.26 days—4 days more than medicine patients'. Mean LOS was high among participants who required long-term IV antibiotics, particularly those with endocarditis or osteomyelitis (21.75 days; range, 1.00-51.00 days). We excluded one outlier with a 116-day hospitalization.

TABLE 1. Needs Assessment Participant Characteristics

Substance Use	n (%)
Total participants	185
Any alcohol use in the past 3 months	109/185 (59)
Any opioid use in the past 3 months	68/185 (37)
Any drug[a] use in the past 3 months	137/185 (74)
Interest in cutting back or quitting	
Alcohol	63/109 (58)
Drugs	92/137 (67)
Moderate – high risk substance use	
Alcohol	82/185 (44)
Amphetamines	74/185 (40)
Opioids	72/185 (39)
Cocaine	23/185 (12)
Past 3 month polysubstance use	113/185 (61)
Interest in MAT for alcohol use disorder among moderate-high risk users	13/82 (16)
Interest in MAT for opioid use disorder among moderate-high risk users	
Any MAT	39/72 (54)
Methadone	26/72 (36)
Buprenorphine	23/72 (32)

[a]Cocaine, amphetamines, inhalants, sedatives, hallucinogens, opioids.

NOTE: Abbreviation: MAT, medications for addiction treatment.

Intervention Design

Mapping needs to intervention components. We mapped needs assessment findings to 3 main IMPACT components: inpatient addiction medicine consultation service, pathways to posthospital SUD treatment, and medically enhanced residential treatment (MERT) (Table 2).

Inpatient addiction medicine consultation service. We developed this service to address patients' report of high readiness to change and interest in starting MAT in the hospital. Community partners highlighted the need for peers to increase engagement and trust. Therefore, we included a physician, a social worker, and two peers on our team. The inpatient service engages patients, advises on withdrawal and pain, performs SUD assessments, initiates MAT, and provides counseling and treatment.

Pathways to posthospital SUD treatment. As pathways from hospital to community SUD treatment were lacking, and long administrative wait times limited access to community treatment, we employed "in-reach" liaisons—community SUD treatment staff who perform in-hospital assessments to triage and coordinate care across systems. Given that patients

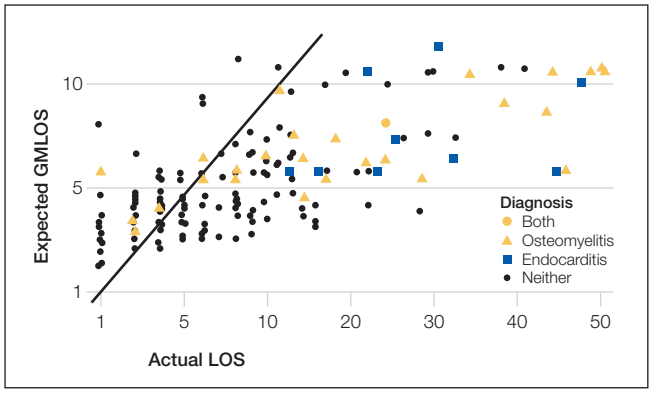

FIG. Hospital LOS among needs assessment patients.

NOTE: Abbreviations: GMLOS, geometric length of stay; LOS, length of stay.

value having treatment choices, we linked pathways to an array of MAT and abstinence-based treatments, including office-based, intensive outpatient and residential levels of care. For patients who live outside the Portland area, we developed relationships with rural stakeholders and engaged the help of the Oregon State Opioid Authority in introducing our program to SUD treatment providers around the state.

Medically Enhanced Residential Treatment (MERT). In many cases where patients required prolonged courses of IV antibiotics, hospital stays were longer for two reasons: At-home central-line self-administration of antibiotics was deemed unsafe, and patients were denied admission to a skilled nursing facility due to history of substance use. These long LOS create an opportunity to initiate and engage patients in treatment, and to render savings by shifting care to a residential addiction treatment setting that can accommodate IV antibiotic administration and MAT. We increased residential staffing and collaborated with a home infusion pharmacy to administer daily infusions on site.

Funding the Intervention

We used administrative data to estimate potential savings and tailored a business case to CCO and hospital payers. The CCO business case centered on hospitalization as an opportunity to engage out-of-treatment adults and potentially reduce high-cost readmissions by managing physical and behavioral health needs. Working within budgeting time lines, we used data from the first 165 participants. These participants had 137 readmissions over a mean observation period of 4.5 months. Mean charge per readmission was $31,157 (range, $699-$206,596) and was highest for people with endocarditis (mean, $55,493; range, $23,204-$145,066) and osteomyelitis (mean, $68,774; range, $29,359-$124,481). We estimated that a 10% reduction in 6-month readmissions could avoid $674,863 in charges.

For the hospital, the primary financial incentive was reduced LOS. Given the possibility of shortening hospitalization through MERT, we estimated a 20% mean LOS reduction; for budgeting, we estimated a conservative 10% reduction. A 10% mean LOS reduction would free 205 bed-days (10% × 10.26 days mean LOS × 200 patients) and create space for another 32 inpatient admissions in year 1, assuming no change from medical patients'

TABLE 2. Key IMPACT Elements, Including Year 1 Enrollment Targets, Staff Descriptions and Roles, and Allocated Resources

Key Findings of Needs Assessment	Program Element and Year 1 Enrollment Target	Staff Descriptions and Roles	Allocated Resource and Staffing Rationale
Hospitalization provides reachable moments OHSU lacked expertise to assess, engage, and initiate SUD treatment Engagement and trust are key	**Hospital-based addiction medicine consultation service** 200 patients	Social worker performs ASAM assessment, uses motivational interviewing to engage patients, initiates evidence-based SUD treatment, and coordinates posthospital addiction care Physician advises on withdrawal and pain management and initiates MAT Peers support patient engagement in hospital and across transition to community SUD care	0.5 FTE physician—half-day weekday coverage based on projection that half the patients would need physician consultation and MAT 1.0 FTE social worker—expected case load of about 6-8 patients/day 1.4 FTE peer mentors—peers would be present 7 days/week, including some evening hours
No pathways from hospital to outpatient addiction treatment Long community wait times	**"In-reach" liaison supports rapid-access pathways to community SUD care after hospital discharge** 100 patients	CADCs from partner organizations "reach in" to hospital, describe community treatment options, support triage and linkage, and serve as points of contact as patients transition across hospital, jail, skilled nursing facility, and community SUD treatment	0.5 FTE CADC—at each partner site
Patients who require long courses of IV antibiotics have very long hospital stays Residential SUD treatment programs not equipped for medically complex patients	**Medically Enhanced Residential Treatment** brings IV antibiotics and nursing care into residential addiction setting 30 patients	Home infusion pharmacy administers daily IV antibiotics and performs weekly central catheter dressing changes Registered nurse supports care coordination and on-site infusion, basic wound care, and other nursing needs Physician prescribes MAT in residential program and provides oversight for medically complex patients Residential program coordinator manages bed flow to support timely access to residential beds Infectious disease team uses video technology to conduct weekly virtual bedside rounds	Payment for 6 days/week home infusion pharmacy costs (insurance plans cover once-weekly home infusion) 0.7 FTE registered nurse 0.1 FTE community addiction physician 0.2 FTE residential program coordinator Hospital infectious disease team supports 30 minutes/week telehealth rounds

NOTE: Abbreviations: ASAM, American Society of Addiction Medicine; CADC, certified alcohol and drug counselor; FTE, full-time equivalent; IMPACT, Improving Addiction Care Team; IV, intravenous; MAT, medication for addiction treatment; OHSU, Oregon Health & Science University; SUD, substance use disorder.

6.26 days mean LOS. The future of bundled payments further bolstered our business case, as did the potential to improve care quality, reduce nonproductive staff time, and increase institutional learning about SUD. Overall program costs approximated projected savings, and the hospital and a local CCO agreed to equally share the costs of the intervention (Table 2).

DISCUSSION

We have described an innovative approach to developing an SUD intervention for hospitalized adults. Using a process of broad stakeholder engagement, data-driven understanding of population needs, and analysis of financial incentives, we built consensus and secured funding for a multicomponent intervention across hospital and post–acute care settings. Other studies have demonstrated the feasibility and efficacy of starting a single medication for a specific indication[7-9] (eg, methadone for opioid use disorder), yet strategies for expanding SUD services in hospitals and facilitating posthospital treatment linkages remain scarce.[21] Our model addresses a widespread need and could be adapted to other hospitals, SUD treatment organizations, and Medicaid payers.

Our experience has several limitations. First, it took place at a single academic medical center in Oregon, a Medicaid expansion state. Second, our needs assessment involved a convenience sample of limited racial/ethnic diversity. Third, almost all patients had insurance, which could limit generalizability. Fourth, to secure funding, it was essential we had a clinical champion who was persuasive with hospital and CCO leadership; though increasing disease burden and skyrocketing costs[2] may drive administrators' increased demand for ways to address SUD in hospitalized adults.

Our experience has several key implications. First, diverse partners were vital at all stages of program design, suggesting hospitals should look beyond traditional healthcare partners to address the SUD epidemic. Second, an interprofessional team that includes physicians, social workers, and peers may better engage patients and address complex system needs. Finally, a planned IMPACT evaluation will assess effects on substance use, healthcare use, and costs.

The United States faces a burgeoning SUD epidemic. Our experience describes an innovative care model and supports the idea that hospitals may play a leading role in convening partners, providing treatment, and driving population health improvements for adults with SUD.

Acknowledgment

The authors would like to acknowledge Peter Rapp and Thomas Yackel for leadership support; Tara Williams for administrative data support; Sarann Bielavitz and Naomi Wright for project management support, and Lynn Smith-Stott and Maria Michalczyk for help with model design. This work was presented at the American Society of Addiction Medicine national conference in Baltimore, MD in April 2016.

Disclosure: This work was funded by Oregon Health & Science University and CareOregon. The authors have no conflicts of interest to disclose.

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Urine Eosinophils for Acute Interstitial Nephritis

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The "Things We Do for No Reason" 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.

Acute interstitial nephritis (AIN) is an important cause of acute kidney injury (AKI) in the hospital setting. However, the diagnosis of AIN is challenging because of its nonspecific clinical manifestations and the invasiveness of kidney biopsy, the gold standard for diagnosis. Urine eosinophils (UEs) emerged several decades ago as a noninvasive alternative for diagnosing AIN. Initial studies found UEs had a significant diagnostic value, but these studies had small sample sizes, and the diagnosis of AIN was made on clinical grounds only, without biopsy confirmation. In this article, we review the literature on the diagnostic value of UEs in the diagnosis of AIN.

CASE REPORT

A 62-year-old woman with type 2 diabetes mellitus, systemic hypertension, coronary artery disease, and obesity is admitted for AKI found on routine laboratory testing. She has been taking amoxicillin and doxycycline for left leg cellulitis the past 5 days, but improvement has been minimal. On admission, blood pressure is 120/74 mm Hg, and heart rate is 89 beats per minute. Serum creatinine level is increased, from 0.7 mg/dL at baseline to 3.6 mg/dL on admission. Complete urinalysis reveals 1+ protein and presence of white blood cells and isormorphic red blood cells. No casts or crystals are seen. Given the possibility of AIN, UE testing is ordered. UEs are positive at 25%. Does this result significantly increase the patient's posttest probability of having AIN?

WHY YOU MIGHT THINK ORDERING URINE EOSINOPHILS IN THE EVALUATION OF AIN IS HELPFUL

AKI occurs in more than 1 in 5 hospitalizations and is associated with a more than 4-fold increased likelihood of in-hospital mortality at 21 days.[1] AIN is an important cause of AKI and has been found in 6% to 30% of AKI patients who had biopsies performed.[2-4] AIN is characterized by infiltration of inflammatory cells in the kidney interstitium and is more commonly caused by drugs, especially beta-lactam antibiotics, and less commonly by autoimmune or systemic diseases and infections. As the signs and symptoms of AIN are nonspecific, and the gold-standard test is renal biopsy, diagnosticians have sought a noninvasive test, such as UEs.

In 1978, Galpin et al.[5] found that UEs comprised 10% to 60% of urine white blood cells in 9 of 9 patients with methicillin-induced interstitial nephritis; 6 of the 9 had biopsy-proven AIN. In 1980, Linton et al.[6] found UEs in 6 of 9 patients with drug-induced AIN; 8 of the 9 had biopsy-proven AIN. In 1986, Nolan et al.[7] reported that, compared with Wright stain, Hansel stain was more sensitive in visualizing UEs; they did not use biopsy for confirmation. Wright-stain detection of UEs is limited by the variable staining characteristics of "eosinophilic" granules in body fluids other than blood. With Hansel stain, UEs are readily identified by their brilliant red-pink granules. These 3 small studies helped make UEs the go-to noninvasive test for assessing for AIN.[8]

WHY THERE IS LITTLE REASON TO ORDER URINE EOSINOPHILS IN PATIENTS WITH SUSPICION FOR AIN

While initial studies indicated UEs might be diagnostically helpful, subsequent studies did not. In 1985, Corwin et al.[9] used Wright stain and found UEs in 65 of 470 adults with AKI. Only 9 (14%) of the 65 had a diagnosis of AIN, which was made mostly on clinical grounds. These findings showed that UEs were produced by other renal or urinary tract abnormalities, such as urinary tract infections, acute tubular necrosis, and glomerulonephritis. In a second study, Corwin et al.[10] found that Hansel stain (vs Wright stain) improved the sensitivity of UEs for AIN diagnosis, from 25% to 62.5%. Sensitivity was improved at the expense of specificity, as Hansel stain was positive in other diagnoses as well. The AIN diagnosis was not confirmed by kidney biopsy in the large majority of patients in this study. Lack of confirmation by biopsy, the gold-standard diagnostic test, was a methodologic flaw of this study and others.

Sutton[11] reviewed data from 10 studies and found AIN could not be reliably excluded in the absence of UEs (only 19 of 32 biopsy-confirmed AIN cases had UEs present). In addition, Ruffing et al.[12] used Hansel stain and concluded

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Received: August 29, 2016; **Revised:** October 27, 2016; **Accepted:** November 1, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2737

TABLE. Urine Eosinophils in the Diagnosis of Acute Interstitial Nephritis

Study	Year	Sample Size, N	AIN			≥1% Urine Eosinophils for the Diagnosis of AIN						
			Diagnosis	Etiology	Prevalence, %	Stain	Sensitivity, %	Specificity, %	PPV, %	NPV, %	LR+	LR–
Corwin et al.[9]	1985	65	Clinical[a]	NS	13.8	Wright	88.9	51.8	22.9	96.7	1.8	0.2
Nolan et al.[7]	1986	92	Clinical[a]	Drugs	12	Hansel	90.9	85.2	45.5	98.6	6.1	0.1
Corwin et al.[10]	1989	183	Clinical[a]	NS	4.4	Hansel	62.5	91.4	25	98.2	7.3	0.4
Ruffing et al.[12]	1994	51	Clinical[a]	Various[b]	29.4	Hansel	40	72.2	37.5	74.3	1.4	0.8
Muriithi et al.[13]	2013	566	Biopsy	Drugs[c]	16.1	Hansel	30.8	68.2	15.6	83.7	0.97	1.01

[a]In large majority of patients, diagnosis of AIN was made on clinical grounds only.

[b]Nonsteroidal anti-inflammatory drugs and other drugs not specified.

[c]In 80% of patients.

NOTE: Abbreviations: AIN, acute interstitial nephritis; LR+, likelihood ratio positive; LR–, likelihood ratio negative; NPV, negative predictive value; NS, not specified; PPV, positive predictive value.

that the positive predictive value of UEs was inadequate in diagnosing AIN. Only 6 of their 15 patients with AIN had positive UEs. Urine eosinophils were also present in patients with other diagnoses (glomerulonephritis, chronic kidney disease, acute pyelonephritis, prerenal azotemia). Like many other investigators, Ruffing et al. made the AIN diagnosis on clinical grounds in the large majority of cases.

Muriithi et al.[13] reported similarly negative results in their retrospective AKI study involving 566 Mayo Clinic patients and spanning almost 2 decades. The study included patients who underwent both Hansel-stain UE testing and kidney biopsy within a week of each other. Only 28 (30%) of 91 biopsy-proven AIN cases were positive for UEs. Using the 1% cutoff for a positive UE test yielded only 30.8% sensitivity and 68.2% specificity. Using the 5% cutoff increased specificity to 91.2%, at the expense of sensitivity (19.2%); positive predictive value improved to only 30%, and negative predictive value remained relatively unchanged, at 85.6%. In short, Muriithi et al. found that UE testing had no utility in AIN diagnosis.

In summary, initial studies, such as those by Corwin et al,[9,10] supported the conclusion that UEs are useful in AIN diagnosis but had questionable validity owing to methodologic issues, including small sample size and lack of biopsy confirmation of AIN. On the other hand, more recent studies, such as the one conducted by Muriithi et al.,[13] had larger sample sizes and biopsy-proven diagnoses and confirmed the poor diagnostic value of UEs in AIN.

The poor sensitivity and specificity of UE tests can have important consequences. A false positive test may cause the clinician to incorrectly diagnose the patient with AIN and prompt the clinician to remove medications that may be vitally important. The clinician may also consider treating the patient with steroids empirically. A false negative test may inappropriately reassure the clinician that the patient does not have AIN and does not need cessation of the culprit drug. This may also lead the clinician to forego a necessary kidney biopsy.

WHAT YOU SHOULD DO INSTEAD

A history of recent exposure to a classic offending drug (eg, beta-lactam, proton pump inhibitor, nonsteroidal anti-inflammatory drug) in combination with the classic triad of fever, rash, and peripheral eosinophilia suggests an AIN diagnosis. However, less than 5% to 10% of patients present with this triad.[14,15] Regardless of the triad's presence, if other causes of AKI have been excluded, stopping a potential offending agent and monitoring for improvement are recommended. If a culprit drug cannot be safely discontinued, renal biopsy may be necessary for confirmation of the diagnosis. Moreover, if kidney function continues to deteriorate, a nephrology consultation may be warranted for guidance on the risks and benefits of performing a kidney biopsy to confirm the diagnosis and/or the use of corticosteroids.

RECOMMENDATIONS

- Urine eosinophils should not be used in the diagnosis of AIN.
- The clinical diagnosis of drug-associated AIN should be based on excluding other possible likely etiologies of AKI and confirming the history of drug exposure. This is reinforced when kidney function improves upon discontinuation of offending agent.
- Kidney biopsy is the gold standard for AIN and should be performed if the clinical picture is unclear or the renal function is not improving upon discontinuation of offending agent.

CONCLUSION

Since the mid-1980s, studies have found that UEs are too insensitive and nonspecific to confirm or exclude the diagnosis of AIN in patients with AKI (Table). UEs are seen in other AKI etiologies, such as pyelonephritis, acute tubular necrosis, atheroembolic renal disease, and glomerulonephritis. Current evidence-based medicine does not support use of UEs as a biomarker for AIN. False-positive and false-negative results confuse the overall picture and result either in discontinuation of important medications and unnecessary steroid treatment or in delayed removal of a culprit medication.[16]

Our case's positive UE test does not affect the posttest probability that our patient has AIN. Presence of a culprit drug and absence of clinical data suggesting an alternative diag-

nosis would lead most clinicians to change antibiotic therapy and observe for improvement in renal function.

Disclosure: Nothing to report.

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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A Practical Framework for Understanding and Reducing Medical Overuse: Conceptualizing Overuse Through the Patient-Clinician Interaction

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Overuse of medical services is an increasingly recognized driver of poor-quality care and high cost. A practical framework is needed to guide clinical decisions and facilitate concrete actions that can reduce overuse and improve care. We used an iterative, expert-informed, evidence-based process to develop a framework for conceptualizing interventions to reduce medical overuse. Given the complexity of defining and identifying overused care in nuanced clinical situations and the need to define care appropriateness in the context of an individual patient, this framework conceptualizes the patient–clinician interaction as the nexus of decisions regarding inappropriate care. This interaction is influenced by other utilization drivers, including healthcare system factors, the practice environment, the culture of professional medicine, the culture of healthcare consumption, and individual patient and clinician factors. The variable strength of the evidence supporting these domains highlights important areas for further investigation. *Journal of Hospital Medicine* 2017;12:346-351. © 2017 Society of Hospital Medicine

Medical services overuse is the provision of healthcare services for which there is no medical basis or for which harms equal or exceed benefits.[1] This overuse drives poor-quality care and unnecessary cost.[2,3] The high prevalence of overuse is recognized by patients,[4] clinicians,[5] and policymakers.[6] Initiatives to reduce overuse have targeted physicians,[7] the public,[8] and medical educators[9,10] but have had limited impact.[11,12] Few studies have addressed methods for reducing overuse, and de-implementation of nonbeneficial practices has proved challenging.[1,13,14] Models for reducing overuse are only theoretical[15] or are focused on administrative decisions.[16,17] We think a practical framework is needed. We used an iterative process, informed by expert opinion and discussion, to design such a framework.

METHODS

The authors, who have expertise in overuse, value, medical education, evidence-based medicine, and implementation science, reviewed related conceptual frameworks[18] and evidence regarding drivers of overuse. We organized these drivers into domains to create a draft framework, which we presented at Preventing Overdiagnosis 2015, a meeting of clinicians, patients, and policymakers interested in overuse. We incorporated feedback from meeting attendees to modify framework domains, and we performed structured searches (using key words in Pubmed) to explore, and estimate the strength of, evidence supporting items within each domain. We rated supporting evidence as strong (studies found a clear correlation between a factor and overuse), moderate (evidence suggests such a correlation or demonstrates a correlation between a particular factor and utilization but not overuse per se), weak (only indirect evidence exists), or absent (no studies identified evaluating a particular factor). All authors reached consensus on ratings.

Framework Principles and Evidence

Patient-centered definition of overuse. During framework development, defining clinical appropriateness emerged as the primary challenge to identifying and reducing overuse. Although some care generally is appropriate based on strong evidence of benefit, and some is inappropriate given a clear lack of benefit or harm, much care is of unclear or variable benefit. Practice guidelines can help identify overuse, but their utility may be limited by lack of evidence in specific clinical situations,[19] and their recommendations may apply poorly to an individual patient. This presents challenges to using guidelines to identify and reduce overuse.

Despite limitations, the scope of overuse has been estimated by applying broad, often guideline-based, criteria for care appropriateness to administrative data.[20] Unfortunately, these estimates provide little direction to clinicians and patients partnering to make usage decisions. During framework development, we identified the importance of a patient-level, patient-specific definition of overuse. This approach reinforces the importance of meeting patient needs while standardizing treatments to reduce overuse. A patient-centered approach may also assist professional societies and advocacy groups in developing actionable campaigns and may uncover evidence gaps.

Centrality of patient-clinician interaction. During framework development, the patient–clinician interaction emerged as

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Received: September 15, 2016; **Revised:** October 26, 2016; **Accepted:** November 10, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2738

TABLE 1. Factors That Contribute to Each Domain of the Framework for Overuse Of Care[a]

Domain	Factors	Evidence	Specific Impact	Likely Magnitude of Effect on Overuse
Culture of healthcare consumption	Consumerism and advocating for one's own health Information found on the internet and through the media General expectations about the appropriate amount and type of care Belief that you get what you pay for	Strength: weak None related to specific factors. Evidence related to: Variations in care[27,55] General enthusiasm for screening[56]	Likely leads to more general utilization, overuse, and use of costlier alternatives	Moderate
Patient factors and experiences	Prior healthcare experiences (patient and family) Demographic factors and education Health literacy and numeracy Patient interactions with health center staff Patient interactions with other clinicians	Strength: weak to strong Evidence related to: Impact of race/ethnicity on overuse and underuse[57,58] Patient expectations[59,60] Patient desire for investigation and answers[61]	Variable; can contribute to overuse or protect against overuse	Moderate Interventions related to with patient demographics not defined
Culture of professional medicine	Influence of broad regulations and metrics Value placed on finding answers, certainty Value placed on doing things Discomfort with discussing/admitting diagnostic uncertainty to others (strong vs. weak) Fear of missing diagnoses New high tech solutions more valued and reimbursed.	Strength: absent to moderate No evidence exploring role of most individual factors. Evidence related to: Association between local culture and overuse[62-64] (moderate evidence) Physician factors and geographic variations[65]	Overuse performance measures can limit overuse but measures for preventing underuse may lead to overuse Emphasis on certainty, technology and active intervention likely contribute to overuse	Moderate to high
Clinician attitudes and beliefs	Personality and personal biases Poor numeracy and knowledge of evidence Past experiences with other patients with the same condition Knowledge of and attitudes toward particular patient Fear of litigation (defensive medicine) Clinician-clinician interactions Clinician-staff interactions Comfort with discussing cost or other issues Discomfort with diagnostic uncertainty	Strength: weak Evidence related to: Physician beliefs and geographic variations[28] Variation in utilization based on specific physician characteristics[66-68] Self-reported drivers of physician overuse[26]	Traditionally mostly push toward more care Poor numeracy, lack of knowledge, discomfort with uncertainty, sampling biases from past experiences, interactions with other clinicians, fear of litigation, and some personality traits likely lead to overuse Patient continuity helps prevent overuse	High
Practice environment	Financial incentives Practice norms within the group and expectations from the affiliated health system Structures which influence specific practices Risk of lawsuits Performance metrics may encourage overuse	Strength: weak Practice norms not well studied Evidence related to: Local cultural norms and aggressive care[69-71] Residency training and utilization[29,72,73] Financial incentives[41,74] (weak evidence) General influence of practice setting[75] Quality metrics may encourage too much care and overuse[76,77]	Local cultural norms are influential (including local training culture) Other factors vary based on specifics	High
The patient-clinician interaction	Specific communication styles Concordance of culture, race, language, and gender Prior experiences with each other Visit priorities	Strength: moderate for shared decision making, continuity, weak for other factors Evidence related to: Continuity of care and overuse[21] Continuity of care and utilization[22,23] Communication[24] Shared decision making and overuse[25]	Continuity of care likely reduces overuse Shared decision making likely reduces overuse Unclear impact of culture and language	High

[a]Likely magnitude of effect on overuse was determined by author consensus based on strength and breadth of evidence and other factors.

the nexus through which drivers of overuse exert influence. The centrality of this interaction has been demonstrated in studies of the relationship between care continuity and overuse[21] or utilization,[22,23] by evidence that communication and patient–clinician relationships affect utilization,[24] and by the observation that clinician training in shared decision-making reduces overuse.[25] A patient-centered framework assumes that, at least in the weighing of clinically reasonable options, a patient-centered approach optimizes outcomes for that patient.

Incorporating drivers of overuse. We incorporated drivers of overuse into domains and related them to the patient–clinician interaction.[26] Domains included the culture of healthcare consumption, patient factors and experiences, the practice environment, the culture of professional medicine, and clinician attitudes and beliefs.

We characterized the evidence illustrating how drivers within each domain influence healthcare use. The evidence

for each domain is listed in Table 1.

RESULTS

The final framework is shown in the Figure. Within the healthcare system, patients are influenced by the culture of healthcare consumption, which varies within and among countries.[27] Clinicians are influenced by the culture of medical care, which varies by practice setting,[28] and by their training environment.[29] Both clinicians and patients are influenced by the practice environment and by personal experiences. Ultimately, clinical decisions occur within the specific patient–clinician interaction.[24] Table 1 lists each domain's components, likely impact on overuse, and estimated strength of supporting evidence. Interventions can be conceptualized within appropriate domains or through the interaction between patient and clinician.

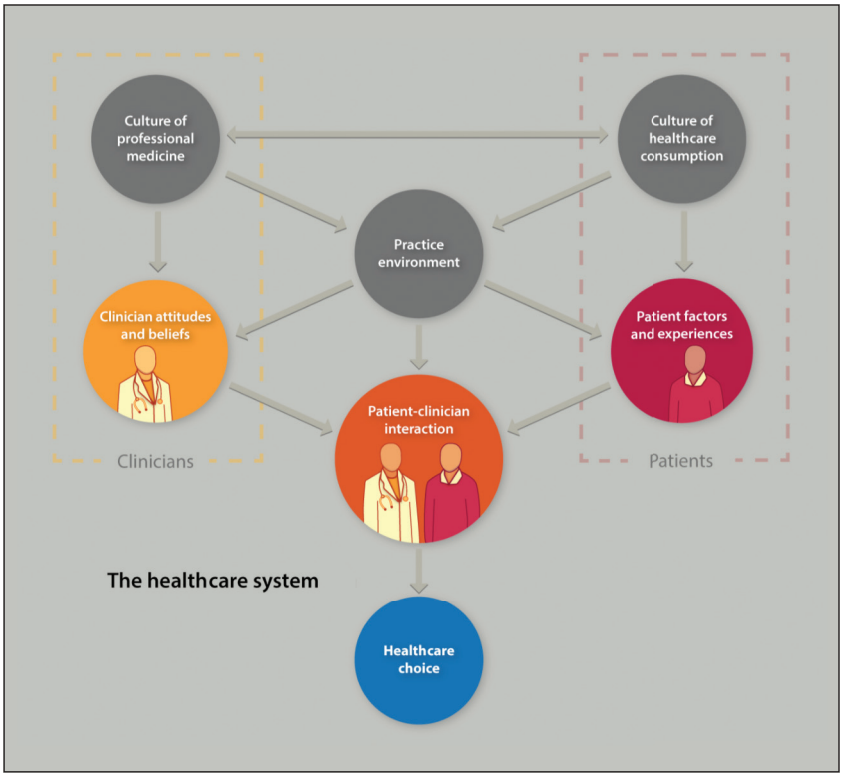

FIG. Framework for understanding and reducing overuse.

DISCUSSION

We developed a novel and practical conceptual framework for characterizing drivers of overuse and potential intervention points. To our knowledge, this is the first framework incorporating a patient-specific approach to overuse and emphasizing the patient–clinician interaction. Key strengths of framework development are inclusion of a range of perspectives and characterization of the evidence within each domain. Limitations include lack of a formal systematic review and broad, qualitative assessments of evidence strength. However, we believe this framework provides an important conceptual foundation for the study of overuse and interventions to reduce overuse.

Framework Applications

This framework, which highlights the many drivers of overuse, can facilitate understanding of overuse and help conceptualize change, prioritize research goals, and inform specific interventions. For policymakers, the framework can inform efforts to reduce overuse by emphasizing the need for complex interventions and by clarifying the likely impact of interventions targeting specific domains. Similarly, for clinicians and quality improvement professionals, the framework can ground root cause analyses of overuse-related problems and inform allocation of limited resources. Finally, the relatively weak evidence on the role of most acknowledged drivers of overuse suggests an important research agenda. Specifically, several pressing needs have been identified: defining relevant physician and patient cultural factors, investigating interventions to impact culture, defining practice environment features that optimize care appropriateness, and describing specific patient–clinician interaction practices that minimize overuse while providing needed care.

Targeting Interventions

Domains within the framework are influenced by different types of interventions, and different stakeholders may target different domains. For example:

- The culture of healthcare consumption may be influenced through public education (eg, Choosing Wisely® patient resources)[30-32] and public health campaigns.
- The practice environment may be influenced by initiatives to align clinician incentives,[33] team care,[34] electronic health record interventions,[35] and improved access.[36]
- Clinician attitudes and beliefs may be influenced by audit and feedback,[37-40] reflection,[41] role modeling,[42] and education.[43-45]
- Patient attitudes and beliefs may be influenced by education, access to price and quality information, and increased engagement in care.[46,47]
- For clinicians, the patient–clinician interaction can be improved through training in communication and shared decision-making,[25] through access to information (eg, costs) that can be easily shared with patients,[48,49] and through novel visit structures (eg, scribes).[50]
- On the patient side, this interaction can be optimized with improved access (eg, through telemedicine)[51,52] or with patient empowerment during hospitalization.
- The culture of medicine is difficult to influence. Change likely will occur through:
  - Regulatory interventions (eg, Transforming Clinical Practice Initiative of Center for Medicare & Medicaid Innovation).

TABLE 2. Using the Framework for Real-Life Examples of Overuse to Identify Practical Ways in Which Overuse Can Be Addressed

Example of overuse	Possible Drivers/Domains	Feasible Approaches to Improvement
A hospitalist on a general medical service wants to reduce use of routine lab testing	Culture of health care: expectation of all clinicians (including attendings, consultants, nursing) for daily lab testing Clinician factors: belief that more is better, poor knowledge of evidence Practice environment: ease of daily ordering in the EMR Patient factors: expectation for frequent testing (likely a minor factor)	Culture: broad campaign across the medical center Clinician: education about evidence/guidelines[43,44] Practice environment: EMR alert[35]
A physician hospital leader wishes to reduce inpatient opioid prescribing	Clinician factors: misperception of patient/parent desires, discomfort with pain treatment[81] Practice environment: pressure to discharge patients leading to aggressive pain treatment Patient factors: poor understanding of the potential harms of opioids, demand Patient-clinician interaction: poor communication regarding pain itself and the benefits/harms of therapy	Clinician: education about guidelines/evidence[43,44] Patient: provide information about options for treating pain and potential opioid harms Patient-clinician interaction: physician-directed tool for communicating about the issue[49]
A palliative care fellow seeks to reduce imaging tests in EOL hospitalized patients	Culture of healthcare: need to define clinical problems even if there is no intervention, discomfort with doing nothing Clinician factors: belief that more information helps patients, belief that patients desire testing Patient factors: poor knowledge or acceptance of prognosis Patient-clinician interaction: poor communication regarding prognosis and EOL preferences	Clinician factors: education about harms of testing in these patients Patient-clinician interaction: specific tools to improve communication about EOL preferences[49,78]

NOTE: Abbreviations: EMR, electronic medical record; EOL, end of life.

- Educational initiatives (eg, high-value care curricula of Alliance for Academic Internal Medicine/American College of Physicians[53]).
- Medical journal features (eg, "Less Is More" in *JAMA Internal Medicine*[54] and "Things We Do for No Reason" in *Journal of Hospital Medicine*).
- Professional organizations (eg, Choosing Wisely®).

As organizations implement quality improvement initiatives to reduce overuse of services, the framework can be used to target interventions to relevant domains. For example, a hospital leader who wants to reduce opioid prescribing may use the framework to identify the factors that encourage prescribing in each domain—poor understanding of pain treatment (a clinician factor), desire for early discharge encouraging overly aggressive pain management (an environmental factor), patient demand for opioids combined with poor understanding of harms (patient factors), and poor communication regarding pain (a patient–clinician interaction factor). Although not all relevant factors can be addressed, their classification by domain facilitates intervention, in this case perhaps leading to a focus on clinician and patient education on opioids and development of a practical communication tool that targets 3 domains. Table 2 lists ways in which the framework informs approaches to this and other overused services in the hospital setting. Note that some drivers can be acknowledged without identifying targeted interventions.

Moving Forward

Through a multi-stakeholder iterative process, we developed a practical framework for understanding medical overuse and interventions to reduce it. Centered on the patient–clinician interaction, this framework explains overuse as the product of medical and patient culture, the practice environment and incentives, and other clinician and patient factors. Ultimately, care is implemented during the patient–clinician interaction, though few interventions to reduce overuse have focused on that domain.

Conceptualizing overuse through the patient–clinician interaction maintains focus on patients while promoting population health that is both better and lower in cost. This framework can guide interventions to reduce overuse in important parts of the healthcare system while ensuring the final goal of high-quality individualized patient care.

Acknowledgments

The authors thank Valerie Pocus for helping with the artistic design of Framework. An early version of Framework was presented at the 2015 Preventing Overdiagnosis meeting in Bethesda, Maryland.

Disclosures: Dr. Morgan received research support from the VA Health Services Research (CRE 12-307), Agency for Healthcare Research and Quality (AHRQ) (K08- HS18111). Dr. Leppin's work was supported by CTSA Grant Number UL1 TR000135 from the National Center for Advancing Translational Sciences, a component of the National Institutes of Health (NIH). Dr. Korenstein's work on this paper was supported by a Cancer Center Support Grant from the National Cancer Institute to Memorial Sloan Kettering Cancer Center (award number P30 CA008748). Dr. Morgan provided a self-developed lecture in a 3M-sponsored series on hospital epidemiology and has received honoraria for serving as a book and journal editor for Springer Publishing. Dr. Smith is employed by the American College of Physicians and owns stock in Merck, where her husband is employed. The other authors report no potential conflicts of interest.

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Rendered Speechless

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.

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A 63-year-old man at an inpatient rehabilitation center was transferred to an academic tertiary care center for evaluation of slurred speech and episodic confusion. He was accompanied by his wife, who provided the history. Three weeks earlier, the patient had fallen, sustaining a right femur fracture. He underwent surgery and was discharged to rehabilitation on postoperative day 3. During the second week of rehabilitation, he developed a cough and low-grade fevers, which prompted treatment with cefpodoxime for 5 days for presumed pneumonia. The day after completing antimicrobial therapy, he became confused and began to slur his words.

Confusion is a nonspecific symptom that typically has a diffuse or multifocal localization within the cerebral hemispheres and is unlikely to be caused by a single lesion. Slurred speech may accompany global metabolic dysfunction. However, slurred speech typically localizes to the brainstem, the cerebellum in the posterior fossa, the nuclei, or the course of cranial nerves VII, X, or XII, including where these nerves pass through the subarachnoid space.

It seems this patient's new neurologic symptoms have some relationship to his fall. Long-bone fractures and altered mental status (AMS) lead to consideration of fat emboli, but this syndrome typically presents in the acute period after the fracture. The patient is at risk for a number of complications, related to recent surgery and hospitalization, that could affect the central nervous system (CNS), including systemic infection (possibly with associated meningeal involvement) and venous thromboembolism with concomitant stroke by paradoxical emboli. The episodic nature of the confusion leads to consideration of seizures from structural lesions in the brain. Finally, the circumstances of the fall itself should be explored to determine whether an underlying neurologic dysfunction led to imbalance and gait difficulty.

Over the next 3 days at the inpatient rehabilitation center, the patient's slurred speech became unintelligible, and he experienced intermittent disorientation to person, place, and time. There was no concomitant fever, dizziness, headache, neck pain, weakness, dyspnea, diarrhea, dysuria, or change in hearing or vision.

Progressive dysarthria argues for an expanding lesion in the posterior fossa, worsening metabolic disturbance, or a problem affecting the cranial nerves (eg, Guillain-Barré syndrome) or neuromuscular junctions (eg, myasthenia gravis). Lack of headache makes a CNS localization less likely, though disorientation must localize to the brain itself. The transient nature of the AMS could signal an ictal phenomenon or a fluctuating toxic or metabolic condition, such as hyperammonemia, drug reaction, or healthcare–acquired delirium.

His past medical history included end-stage liver disease secondary to nonalcoholic steatohepatitis status post transjugular intrahepatic portosystemic shunt (TIPS) procedure three years prior, hepatic encephalopathy, diabetes mellitus type 2, hypertension, previous melanoma excision on his back, and recurrent Clostridium difficile colitis. Two years prior to admission he had been started on an indefinite course of metronidazole 500 mg twice daily without any recurrence. The patient's other medications were aspirin, furosemide, insulin, lactulose, mirtazapine, pantoprazole, propranolol, spironolactone, and zinc. At the rehabilitation center, he was prescribed oral oxycodone 5 mg as needed every 4 hours for pain. He denied use of tobacco, alcohol, and recreational drugs. He previously worked as a funeral home director and embalmer.

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Received: April 13, 2016; **Revised**: September 26, 2016; **Accepted**: October 5, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2739

Hyperammonemia and hepatic encephalopathy can present with a fluctuating mental state that often correlates to dietary protein intake or the frequency of bowel movements; the previous TIPS history places the patient at further risk. Use of oxycodone or another narcotic commonly leads to confusion, , especially in patients who are older, have preexisting cognitive decline, or have concomitant medical comorbidities. Mirtazapine and propranolol have been associated more rarely with encephalopathy, and therefore a careful history of adherence, drug interactions, and appropriate dosing should be obtained. Metronidazole is most often associated neurologically with a peripheral neuropathy; however, it is increasingly recognized that some patients can develop a CNS syndrome that features an AMS, which can be severe and accompanied by ataxia, dysarthria, and characteristic brain magnetic resonance imaging (MRI) findings, including hyperintensity surrounding the fourth ventricle on T_2-weighted images.

Embalming fluid has a high concentration of formaldehyde, and a recent epidemiologic study suggested a link between formaldehyde exposure and increased risk for amyotrophic lateral sclerosis (ALS). ALS uncommonly presents with isolated dysarthria, but its bulbar form can, usually over a much longer course than is demonstrated here. Finally, the patient's history of melanoma places him at risk for stroke from hypercoagulability as well as potential brain metastases or carcinomatous meningitis.

Evaluation was initiated at the rehabilitation facility at the onset of the patient's slurred speech and confusion. Physical examination were negative for focal neurologic deficits, asterixis, and jaundice. Ammonia level was 41 µmol/L (reference range, 11-35 µmol/L). Noncontrast computed tomography (CT) of the head showed no signs of acute infarct or hemorrhage. Symptoms were attributed to hepatic encephalopathy; lactulose was up-titrated to ensure 2 or 3 bowel movements per day, and rifaximin was started.

Hyperammonemia is a cause of non-inflammatory relapsing encephalopathy, but an elevated level is neither a sensitive nor specific indicator of hepatic encephalopathy. Levels of ammonia can fluctuate widely during the day based on the frequency of bowel movements as well as dietary protein intake. In addition, proper handling of samples with prompt delivery to the laboratory is essential to minimize errors.

The ammonia level of 41 µmol/L discovered here is only modestly elevated, but given the patient's history of TIPS as well as the clinical picture, it is reasonable to aggressively treat hepatic encephalopathy with lactulose to reduce ammonia levels. If he does not improve, an MRI of the brain to exclude a structural lesion and spinal fluid examination looking for inflammatory or infectious conditions would be important next steps. Although CT excludes a large hemorrhage or mass, this screening examination does not visualize many of the findings of the metabolic etiology and the other etiologies under consideration here.

Despite 3 days of therapy for presumed hepatic encephalopathy, the patient's slurred speech worsened, and he was transferred to an academic tertiary care center for further evaluation. On admission, his temperature was 36.9°C, heart rate was 80 beats per minute, blood pressure was 139/67 mm Hg, respiratory rate was 10 breaths per minute, and oxygen saturation was 99% on room air. He was alert, awake, and oriented to person, place, and time. He was not jaundiced. He exhibited a moderate dysarthria characterized by monotone speech, decreased volume, decreased breath support, and a hoarse vocal quality with intact language function. Motor control of the lips, tongue, and mandible were normal. Motor strength was 5/5 bilaterally in the upper and lower extremities with the exception of right hip flexion, which was 4/5. The patient exhibited mild bilateral dysmetria on finger-to-nose examination, consistent with appendicular ataxia of the upper extremities. Reflexes were depressed throughout, and there was no asterixis. He had 2+ pulses in all extremities and 1+ pitting edema of the right lower extremity to the mid leg. Pulmonary examination revealed inspiratory crackles at the left base. The rest of the examination findings were normal.

The patient's altered mental state appears to have resolved, and the neurological examination is now mainly characterized by signs that point to the cerebellum. The description of monotone speech typically refers to loss of prosody, the variable stress or intonation of speech, which is characteristic of a cerebellar speech pattern. The hoarseness should be explored to determine if it is a feature of the patient's speech or is a separate process. Hoarseness may involve the vocal cord and therefore, potentially, cranial nerve X or its nuclei in the brainstem. The appendicular ataxia of the limbs points definitively to the cerebellar hemispheres or their pathways through the brainstem.

Unilateral lower extremity edema, especially in the context of a recent fracture, raises the possibility of deep vein thrombosis. If this patient has a right-to-left intracardiac or intrapulmonary shunt, embolization could lead to an ischemic stroke of the brainstem or cerebellum, potentially causing dysarthria.

Laboratory evaluation revealed hemoglobin level of 10.9 g/dL, white blood cell count of 5.3×10^9/L, platelet count of 169×10^9/L, glucose level of 177 mg/dL, corrected calcium level of 9.0 mg/dL, sodium level of 135 mmol/L, bicarbonate level of 30 mmol/L, creatinine level of 0.9 mg/dL, total bilirubin level of 1.3 mg/dL, direct bilirubin level of 0.4 mg/dL, alkaline phosphatase level of 503 U/L, alanine aminotransferase level of 12 U/L, aspartate aminotransferase level of 33 U/L, ammonia level of 49 µmol/L (range, 0-30 µmol/L), international normalized ratio of 1.2, and troponin level of <0.01 ng/mL. Electrocardiogram showed normal sinus rhythm.

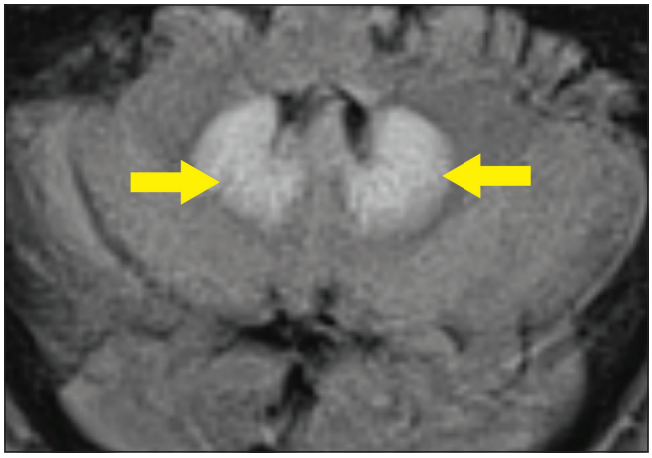

FIG 1. Magnetic resonance imaging shows T_2 hyperintensity of dentate nuclei bilaterally.

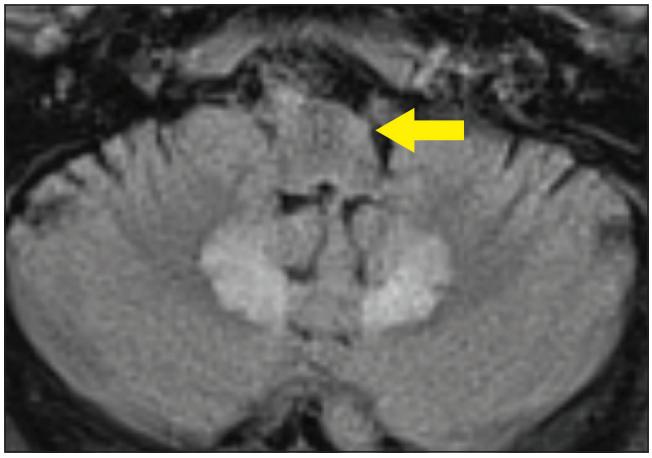

FIG 2. Magnetic resonance imaging shows T_2 hyperintensity of left inferior olivary nuclei.

Some patients with bacterial meningitis do not have a leukocytosis, but patients with meningitis caused by seeding from a systemic infection nearly always do. In this patient's case, lack of a leukocytosis makes bacterial meningitis very unlikely. The elevated alkaline phosphatase level is expected, as this level peaks about 3 weeks after a long-bone fracture and returns to normal over a few months.

Non-contrast CT scan of the head performed on admission demonstrated no large vessel cortical-based infarct, intracranial hemorrhage, hydrocephalus, mass effect, midline shift, or extra-axial fluid. There was mild cortical atrophy as well as very mild periventricular white matter hypodensity.

The atrophy and mild white-matter hypodensities seen on repeat noncontrast CT are nonspecific for any particular entity in this patient's age group. MRI is more effective in evaluating toxic encephalopathies, including metronidazole toxicity or Wernicke encephalopathy, and in characterizing small infarcts or inflammatory conditions of the brainstem and cerebellum, which are poorly evaluated by CT due to the bone surrounded space of the posterior fossa. An urgent lumbar puncture is not necessary due to the slow pace of illness, lack of fever, nuchal rigidity, or serum elevated white blood cell count. Rather, performing MRI should be prioritized. If MRI is nondiagnostic, then spinal fluid should be evaluated for evidence of an infectious, autoimmune, paraneoplastic, or neoplastic process.

MRI was subsequently performed. It showed symmetric abnormal T_2 hyperintensities involving dentate nuclei (Figure 1), left inferior olivary nuclei (Figure 2), restiform bodies, pontine tegmentum, superior cerebellar peduncles, oculomotor nuclei, and subthalamic nuclei. The most prominent hyperintensity was in the dentate nuclei.

The clinical and radiographic features confirm a diagnosis of metronidazole-associated CNS neurotoxicity. The reason for the predilection for edema in these specific areas of the brainstem and midline cerebellum is unclear but likely is related to selective neuronal vulnerability in these structures. The treatment is to stop metronidazole. In addition, the fluctuating mental status should be evaluated with electroencephalogram to ensure concomitant seizures are not occurring.

These MRI findings were consistent with metronidazole toxicity. Metronidazole was discontinued, and 2 days later the patient's speech improved. Two weeks after medication discontinuation, his speech was normal. There were no more episodes of confusion.

DISCUSSION

Metronidazole was originally developed in France during the 1950s as an anti-parasitic medication to treat trichomonas infections. In 1962, its antibacterial properties were discovered after a patient with bacterial gingivitis improved while taking metronidazole for treatment of *Trichomonas vaginalis*.[1] Since that time metronidazole has become a first-line treatment for anaerobic bacteria and is now recommended by the Infectious Diseases Society of America[2] and the American College of Gastroenterology[3] as a first-line therapy for mild and moderate C *difficile* infections.

Common side effects of metronidazole are nausea, vomiting, decreased appetite, diarrhea, headaches, peripheral neuropathy, and metallic taste; less common is CNS toxicity. Although the incidence of CNS toxicity is unknown, a systematic review of the literature found 64 cases reported between 1965 and 2011.[4] CNS toxicity most often occurs between the fifth and sixth decades of life, and about two thirds of the people affected are men.[4] CNS adverse effects characteristically fall into 4 categories: cerebellar dysfunction (eg, ataxia, dysarthria, dysmetria, nystagmus; 75%), AMS (33%), seizures (13%), and a combination of the first 3 categories.[4]

The exact mechanism of metronidazole CNS toxici-

ty is unknown, but vasogenic or cytotoxic edema may be involved.[5,6] Other potential etiologies are neural protein inhibition, reversible mitochondrial dysfunction, and modifications of the inhibitory neurotransmitter gamma-aminobutyric acid receptor in the cerebellum.[7,8] There is no known genetic predisposition. Although the risk for CNS toxicity traditionally is thought to correlate with therapy duration and cumulative dose,[7,9] in 2011 a systemic review found no significant correlation.[4] In fact, 26% of patients with CNS toxicity were treated with metronidazole for less than 1 week at time of diagnosis.[4]

Brain CT is typically normal. On brain MRI, lesions most commonly appear as bilateral symmetric T_2 hyperintensities, most often in the cerebellar dentate nuclei (85%) and less often in the midbrain (55%), the splenium of the corpus callosum (50%), the pons (35%), and the medulla (30%).[4,10] Radiographic changes have been noted as early as 3 days after symptom onset. Based on damage severity and area affected (white or gray matter), vasogenic edema and cytotoxic edema may in combination be contributing to MRI abnormalities.[6,10] Hyperintensities of the bilateral dentate nuclei can help in distinguishing metronidazole-induced encephalopathy from other potential disease processes, such as Wernicke encephalopathy.[10]

The prognosis for patients with metronidazole-induced neurotoxicity is favorable if metronidazole is discontinued. Approximately two-thirds of patients will have complete resolution of symptoms, which is more commonly observed when patients present with seizures or altered mental status. Approximately one-third will show partial improvement, particularly if the symptoms are due to cerebellar dysfunction. It is rare to experience permanent damage or death.[4] Neurologic recovery usually begins within a week after medication discontinuation but may take months for complete recovery to occur.[6,8,9,11] Follow-up imaging typically shows reversal of the original lesions, but this does not always correlate with symptom improvement.[4,10]

Despite its frequent use and long history, metronidazole can have potentially severe toxicity. When patients who are taking this medication present with new signs and symptoms of CNS dysfunction, hospitalists should include metronidazole CNS toxicity in the differential diagnosis and, if they suspect toxicity, have a brain MRI performed. Hospitalists often prescribe metronidazole because of the increasing number of patients being discharged from acute-care hospitals with a diagnosis of C *difficile* colitis.[12] Brain MRI remains the imaging modality of choice for diagnosis. Discontinuation of metronidazole is usually salutary in reversing symptoms. Being keenly aware of this toxicity will help clinicians avoid being rendered speechless by a patient rendered speechless.

TEACHING POINTS

- CNS toxicity is a rare but potentially devastating side effect of metronidazole exposure.
- Metronidazole CNS adverse effects characteristically fall under 4 categories:
  - Cerebellar dysfunction, such as ataxia, dysarthria, dysmetria, or nystagmus (75%).
  - AMS (33%).
  - Seizures (13%).
  - A combination of the first 3 categories.
- Typically lesions indicating metronidazole toxicity on brain MRI are bilateral symmetric hyperintensities on T2-weighted imaging in the cerebellar dentate nuclei, corpus callosum, midbrain, pons, or medulla.
- Treatment of CNS toxicity is metronidazole discontinuation, which results in a high rate of symptom resolution.

Disclosure: Nothing to report.

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Systematic Review of Interventions to Reduce Urinary Tract Infection in Nursing Home Residents

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BACKGROUND: Urinary tract infections (UTIs) in nursing homes are common, costly, and morbid.

PURPOSE: Systematic literature review of strategies to reduce UTIs in nursing home residents.

DATA SOURCES: Ovid MEDLINE, Cochrane Library, CINAHL, Web of Science and Embase through June 22, 2015.

STUDY SELECTION: Interventional studies with a comparison group reporting at least 1 outcome for: catheter-associated UTI (CAUTI), UTIs not identified as catheter-associated, bacteriuria, or urinary catheter use.

DATA EXTRACTION: Two authors abstracted study design, participant and intervention details, outcomes, and quality measures.

DATA SYNTHESIS: Of 5794 records retrieved, 20 records describing 19 interventions were included: 8 randomized controlled trials, 10 pre-post nonrandomized interventions, and 1 nonrandomized intervention with concurrent controls. Quality (range, 8-25; median, 15) and outcome definitions varied greatly. Thirteen studies employed strategies to reduce catheter use or improve catheter care; 9 studies employed general infection prevention strategies (eg, improving hand hygiene, surveillance, contact precautions, reducing antibiotics). The 19 studies reported 12 UTI outcomes, 9 CAUTI outcomes, 4 bacteriuria outcomes, and 5 catheter use outcomes. Five studies showed CAUTI reduction (1 significantly); 9 studies showed UTI reduction (none significantly); 2 studies showed bacteriuria reduction (none significantly). Four studies showed reduced catheter use (1 significantly).

LIMITATIONS: Studies were often underpowered to assess statistical significance; none were pooled given variety of interventions and outcomes.

CONCLUSIONS: Several practices, often implemented in bundles, such as improving hand hygiene, reducing and improving catheter use, managing incontinence without catheters, and enhanced barrier precautions, appear to reduce UTI or CAUTI in nursing home residents. *Journal of Hospital Medicine* 2017;12:356-368. © 2017 Society of Hospital Medicine

Given the limited number of geriatricians in the U.S., hospitalists commonly manage nursing home residents admitted for post-acute care.[1-4] Urinary tract infection (UTI) is one of the most common infections in nursing homes, often leading to sepsis and readmission to acute care.[5] Inappropriate use of antibiotics to treat asymptomatic bacteriuria is both common and hazardous to nursing home residents.[6] Up to 10% of nursing home residents will have an indwelling urinary catheter at some point during their stay.[7-9] Residents with indwelling urinary catheters are at increased risk for catheter-associated urinary tract infection (CAUTI) and bacteriuria, with an estimated 50% of catheterized residents developing symptomatic CAUTI.[5] While urinary catheter prevalence is lower in nursing homes than in the acute care setting, duration of use is often prolonged.[7,10] In a setting where utilization is low, but use is prolonged, interventions designed to reduce UTI in acutely ill patients[11] may not be as helpful for preventing infection in nursing home residents.

Our objective was to review the available evidence to prevent UTIs in nursing home residents to inform both bedside care and research efforts. Two types of literature review and summary were performed. First, we conducted a systematic review of individual studies reporting outcomes of UTI, CAUTI, bacteriuria, or urinary catheter use after interventions for reducing catheter use, improving insertion and maintenance of catheters, and/or general infection prevention strategies (eg, improving hand hygiene, infection surveillance, contact precautions, standardizing UTI diagnosis, and antibiotic use). Second, we performed a narrative review to generate an overview of evidence and published recommendations in both acute care and nursing home settings to prevent UTI in catheterized and non-catheterized older adults, which is provided as a comprehensive reference table for clinicians and researchers choosing and refining interventions to reduce UTIs.

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Additional Supporting Information may be found in the online version of this article.

Received: July 22, 2016; **Revised:** October 7, 2016; **Accepted:** October 18, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2724

METHODS

The systematic review was performed according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis recommendations. The protocol was registered at the PROSPERO International Prospective Register of Systematic Reviews, (CRD42013005787). The narrative review was performed using the articles obtained from the systematic search and a targeted literature review by topic for a comprehensive list of interventions, including other interventions summarized in published reviews and guidelines.

Eligibility Criteria Review

Study Design. To address the breadth and depth of literature available to inform interventions to prevent UTI in nursing homes, broad eligibility criteria were applied with the expectation of varied designs and outcomes. All included studies for the systematic review were published manuscripts reporting a comparison group. We included randomized controlled trials as well as nonrandomized trials (pretest/posttest, with or without concurrent or nonconcurrent controls), with any duration of postintervention follow-up. Observational and retrospective studies were excluded.

Participants. We were interested in interventions and outcomes reported for nursing homes, defined as facilities providing short-stay skilled nursing care and/or rehabilitation, as well as long-term care. We also included evidence derived from rehabilitation facilities and spinal cord injury programs focused on reducing CAUTI risk for chronically catheterized residents. We excluded long-term acute care hospitals, hospice, psychiatric/mental health facilities, pediatric, and community dwelling/outpatient settings.

Interventions. We included interventions involving urinary catheter use such as improving appropriate use, aseptic placement, maintenance care, and prompting removal of unnecessary catheters. We included infection prevention strategies with a particular interest in hand hygiene, barrier precautions, infection control strategies, infection surveillance, use of standardized infection definitions, and interventions to improve antibiotic use. We included single and multiple interventions.

Outcomes

1. Healthcare-associated urinary tract infection: UTI occurring after admission to a healthcare facility, not identified specifically as catheter-associated. We categorized UTI outcomes with as much detail as provided, such as whether the reported outcome included only noncatheter-associated UTIs, the time required after admission (eg, more than 2 days), and whether the UTIs were defined by only laboratory criteria, clinically diagnosed infections, symptomatic, or long-term care specific surveillance definitions.

2. Catheter-associated urinary tract infection: UTI occurring in patients during or immediately after use of a urinary catheter. We noted whether CAUTI was defined by laboratory criteria, clinical symptoms, provider diagnosis, or antimicrobial treatment for case identification. We were primarily interested in CAUTI developing after placing an indwelling urinary catheter, commonly known as a Foley, but also in CAUTI occurring with other catheter types such as intermittent straight catheters, external or "condom" catheters, and suprapubic catheters.

3. Bacteriuria: We included the laboratory-based definition of bacteriuria as an outcome to include studies that reduced asymptomatic bacteriuria.

4. Urinary catheter use measures: This includes measures such as urinary catheter utilization ratios (catheter-days/patient-days), prevalence of urinary catheter use, or percentage of catheters with an appropriate indication.

Study Characteristics for Inclusion. Our systematic search included published papers in the English language. We did not exclude studies based on the number of facilities included or eligible, residents/patients included (based on age, gender, catheter use or type, or antibiotic use), intervention details, study withdrawal, loss to follow-up, death, or duration of pre-intervention and postintervention phases.

Data Sources and Searches

The following data sources were searched: Ovid MEDLINE (1950 to June 22, 2015), Cochrane Library via Wiley (1960 to June 22, 2015), CINAHL (1981 to June 22, 2015), Web of Science (1926 to June 22, 2015), and Embase.com (1946 to June 22, 2015). Two major systematic search strategies were performed for this review (Figure). Systematic search 1 was designed broadly using all data sources described above to identify interventions aimed at reducing all UTI events (defined under "*Outcomes*" above) or urinary catheter use (all types), focusing on interventions evaluated in nursing homes. Systematic search 2 was conducted in Ovid MEDLINE to identify studies to reduce UTI events or urinary catheter use measures for patients with a history of long-term or chronic catheter use, including nursing homes and other post-acute care settings such as rehabilitation units or hospitals and spinal cord injury programs, which have large populations of patients with chronic catheter needs. To inform the completeness of the broader systematic searches, supplemental systematic search strategies were performed for specific topics including hydration (supplemental search 1), published work by nursing home researchers known to the authors (supplemental search 2), and contact precautions (supplemental search 3). Search 1 is available at http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013005787. Full search strategies for search 2 and supplemental searches are available upon request.

Study Selection

One author performed an initial screen of all records retrieved by the systematic searches by title and abstract and applied the initial exclusions (eg, non-human, no outcomes of interest), identified duplicate records, and assigned potentially relevant studies into groups such as review articles, epidemiology, interventions, and articles requiring further text review before categorization (Figure). After initial screening, Dr. Meddings reviewed the records by title/abstract. Reference

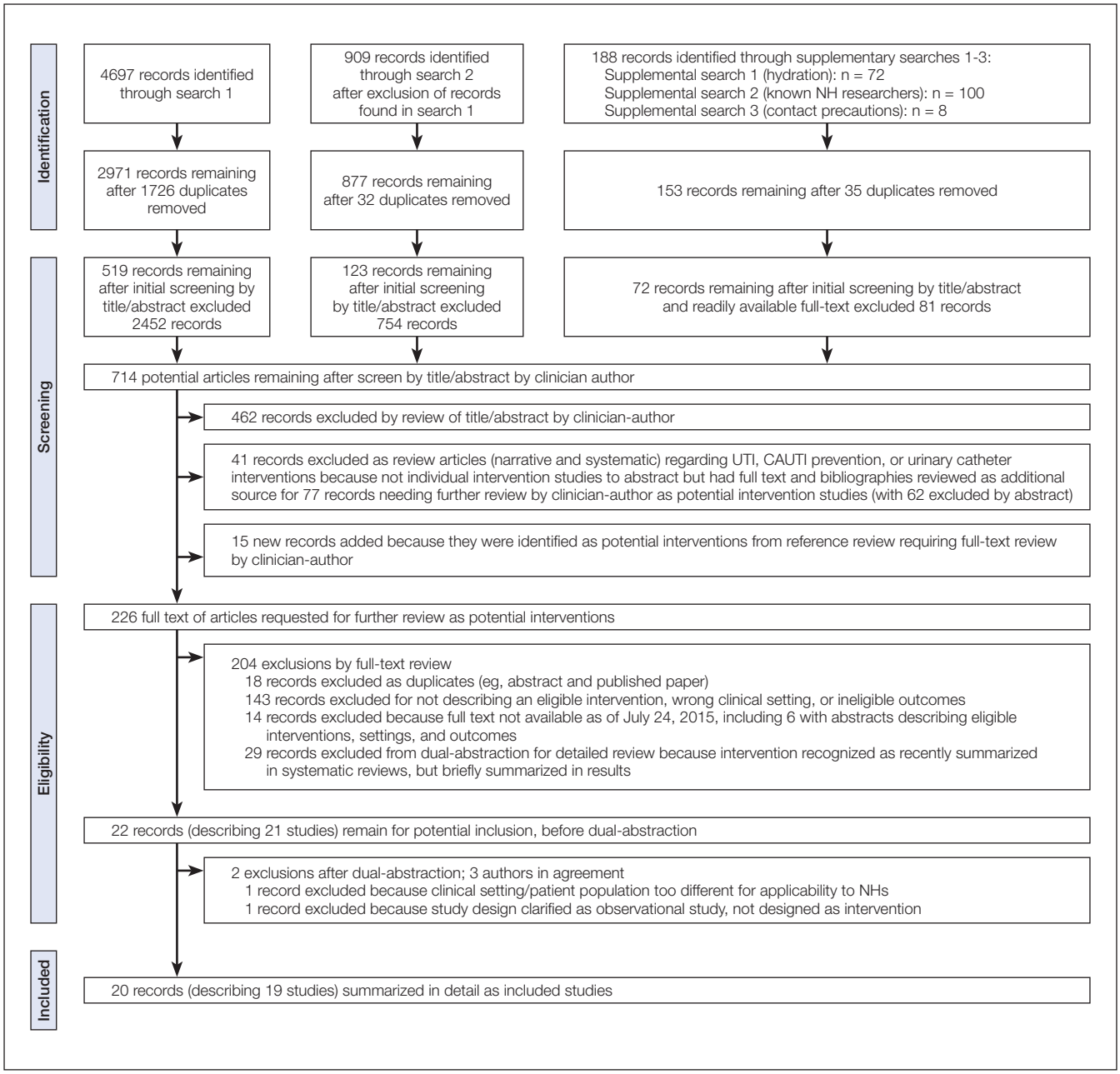

FIG. Study Flow Diagram.

NOTE: Abbreviations: CAUTI, catheter-associated urinary tract infection; NH, nursing home; UTI, urinary tract infection.

lists were reviewed for potential articles for inclusion. Full-text article review informed the selection of those for dual abstraction and quality scoring performed by 2 authors, with discrepancies resolved by a third author. We requested additional information from authors from whom our search had generated only an abstract or brief report, or when additional information such as pre-intervention data was needed.[12-18]

Data Extraction and Quality Assessment

Relevant data regarding study design, participants, inclusion/exclusion criteria, outcomes, and quality criteria were abstracted independently by 2 authors. Methodological quality scores were assigned using a modification of the Quality index checklist developed by Downs and Black appropriate for assessing both randomized and nonrandomized studies of healthcare interventions.[19] We also reviewed study funding sources and other potential quality concerns.

Data Analysis

Due to large trial heterogeneity among these studies about interventions and outcomes reported, outcome data could not be combined into summary measures for meta-analysis to give overall estimates of treatment effects.

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TABLE 1. Characteristics of Included Studies

First Author, Year, Country	Study Design	Participants/Setting Total N if provided	Interventions to Reduce UTI, CAUTI or Urinary Catheter Use[a]			Reported Outcomes Types[b]
			Strategies to reduce or improve catheter use	Infection prevention strategies	Other strategies	
Studies including participants who could be with or without urinary catheterization (ie, not limited to catheterized patients only)						
Ahlbrecht, 1999, U.S.[20]	Pre-post NRT	Residents of a 220-bed community nursing home	Maintenance	Antibiotic review, hand hygiene, infection control, standardize UTI diagnosis, surveillance	Improve resident/patient hygiene	UTI
Brownhill, 2013, United Kingdom[15]	Pre-post NRT	Residents of 47 care homes	Maintenance, catheter securement, standard supplies, incontinence care, other: more leg/night bag sizes, improve urine sampling	Antibiotic use review, standard UTI diagnosis definitions	Programs to reduce falls and pressure ulcers	UTI, CAUTI
Cools, 1988, The Netherlands[21]	Pre-post NRT	320-bed skilled nursing facility	Appropriate indications, prompt removal, incontinence care	Antibiotic guide, hand hygiene, infection control, standardize UTI definitions, surveillance.	Weekly data and new patient review by physicians; improve ventilation by chairs, exercise, physiotherapy	UTI, catheter use
Fendler, 2002, U.S.[22]	NRT with concurrent internal and external controls	Residents of a 275-bed extended care facility providing rehabilitation and subacute care	None specified	Hand hygiene	None specified	CAUTI
Klay, 2005, U.S.[23]	Pre-post NRT of same patients	42 female residents with urinary incontinence in 1 extended care facility	Incontinence care	None specified	Family education on incontinence	UTI
Lin, 2013, Taiwan[24]	Pre-post NRT with external controls	Incontinent residents of 6 nursing homes	None specified	None specified	Increase hydration	Bacteriuria
McConnell, 1984, U.S.[25]	Pre-post NRT	102 residents of nursing home	Appropriate indications, prompt removal Incontinence care	None specified	Increase hydration, ambulation program	UTI
Mentes, 2003, U.S.[26]	RCT-cluster (randomized at facility level)	42 elderly residents from 4 nursing homes (2 VA nursing homes, 2 community nursing homes)	None specified	None specified	Increase hydration	UTI
Miller, 2014, U.S.[27]	Pre-post NRT panel survey of stratified proportionate random sample of nursing directors and administrators compared to resident outcomes	824 nursing homes in large study on implementation of culture change between 2005-2010	Comprehensive "culture change program" anticipated to improve measures including percentage on bladder training programs and reduction of UTI events	None specified	Introduction of "culture change practices," as quantified by a culture change practice score reflecting 3 domains: nursing home environment, resident-centered care involving bladder training programs, staff empowerment	UTI
Stuart, 2015, Australia[28]	Pre-post NRT	Residents in 2 urban aged care facilities; 130 beds	None specified	Nurse-led antibiotic stewardship program, infection control, and surveillance programs	Nurse-physician communications about antibiotics and data	UTI
Van Gaal, 2011, The Netherlands[29,30]	RCT-cluster (randomized at ward level)	392 residents from 10 wards in 6 nursing homes	Hand hygiene/gloves for catheter/bag contact, appropriate indications, standard catheter supplies, maintenance, catheter securement, prompt removal, incontinence care	Surveillance	Fall, pressure ulcer, UTI prevention programs with nurse education/feedback	UTI Catheter use
Yeung, 2011, China[31]	RCT-cluster (randomized at facility level), unblended	1268 elderly residents in 6 nursing homes	None specified	Hand hygiene	None specified	UTI
Studies including only catheterized participants or in settings where very high urinary catheterization rates expected						
Darouiche, 2006, U.S.[32]	RCT single-blind	127 adults with spinal cord injury with long-term indwelling catheters, 4 hospitals	Catheter securement by StatLock device (C.R. Bard, Inc., Covington, Georgia)	None specified	None specified	CAUTI
Evans, 2013, U.S.[33]	Pre-post NRT	22 VA acute care spinal cord injury units	None specified	MRSA bundle of surveillance, contact precautions, hand hygiene	Institutional culture change	UTI

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TABLE 1. Characteristics of Included Studies (continued)

First Author, Year, Country	Study Design	Participants/Setting Total N if provided	Interventions to Reduce UTI, CAUTI or Urinary Catheter Use[a]			Reported Outcomes Types[b]
			Strategies to reduce or improve catheter use	Infection prevention strategies	Other strategies	
Mody, 2015, U.S.[34]	RCT-cluster (randomized at facility level)	418 residents with devices (catheters or feeding tubes) in 12 community nursing homes	Hand hygiene promotion including gown/gloves when working with indwelling devices	Standardize UTI diagnosis, hand hygiene/gown/gloves with morning/evening patient care, splashing activity, MDRO-active surveillance, pre-emptive barrier precautions if device	Staff program education	CAUTI
Priefer, 1982, U.S.[35]	RCT	17 male residents with indwelling catheters in 1 VA nursing home	Scheduled catheter change (monthly + for block/infection) compared to change only for block/infection	None specified	None specified	CAUTI
Saint, 2006, U.S.[36]	RCT unblinded	75 men >40 years requiring a urinary collection device in 1 VA hospital's units (medicine, neuro, rehab, nursing home)	Condom catheterization vs. indwelling Foley catheterization	None specified	None specified	Bacteriuria, and composite of bacteriuria or CAUTI or death
Suardi, 2001, Italy[37]	Pre-post NRT, for same patients	20 spinal cord injury rehab patients with neurogenic bladder with intermittent catheterization	Time-volume dependent catheterization using bladder scanner	None specified	None specified	Catheter use
Tang, 2006, China[38]	RCT	81 females with urinary retention in geriatric rehab ward	Comparing intermittent vs. indwelling catheters, bladder scan protocol	None specified	None specified	CAUTI, bacteriuria

[a]Supplemental Table 2 provides details of the interventions, duration of study, and measure collection details.

[b]UTI: urinary tract infection not identified specifically as catheter-associated; bacteriuria: bacteriuria, not otherwise identified as UTI or CAUTI; outcome results provided in Table 2.

NOTE: Abbreviations: CAUTI: catheter-associated urinary tract infection; MDRO, multidrug resistant organism; MRSA, methicillin-resistant *Staphylococcus aureus;* NRT, nonrandomized trial; RCT, randomized controlled trial; VA, Veterans Affairs.

RESULTS

Systematic Search Results and Study Selection

As detailed in the study flow diagram (Figure), 5794 total records were retrieved by systematic search 1 (4697 studies), search 2 (909 studies), and supplemental searches (188 studies). Hand searching of reference lists of 41 reviews (including narrative and systematic reviews) yielded 77 additional studies for consideration. Twenty-nine records on interventions that were the focus of systematic reviews, including topics of cranberry use, catheter coatings, antimicrobial prophylaxis, washout/irrigation strategies, and sterile versus clean intermittent straight catheterization, were excluded from dual abstraction. Two records were excluded after team discussion of the dual-abstraction results, because 1 study did not meet criteria as an intervention study and 1 study's setting was not applicable in nursing homes. A total of 20 records[15,20-38] (in which 19 studies were described) were selected for final inclusion for detailed assessment and reporting for the systematic review.

Characteristics of Included Studies

Table 1 describes the 19 intervention studies in terms of design, participants, setting, and whether the study included specific categories of interventions expected to decrease UTI or catheter use. These studies included 8 randomized controlled trials (4 with cluster-randomization at the facility or unit level), 10 pre-post nonrandomized interventions, and 1 nonrandomized intervention with concurrent controls. Twelve studies included participants with or without catheters (ie, not limited to catheterized patients only) in nursing homes.[15,20-31] Seven[32-38] studies included catheterized patients only or settings with high expected catheterization rates; settings for these studies included spinal cord units (n=3), nursing homes (n=2), rehabilitation ward (n=1) and VA hospital (n=1), including acute care, nursing home, and rehabilitation units. Total quality scores for the studies ranged from 8 to 25 (median, 15), detailed in Supplemental Table 1.

As detailed in Table 1 and Supplemental Table 2, 7 studies[22,24,26,31,32,35,36] involved single interventions and 12 studies[15,20,21,23,25,27-30,33,34,37,38] included multiple interventions. Interventions to impact catheter use and care were evaluated in 13 studies, including appropriateness of use,[21,25,29,30] improving catheter maintenance care,[15,20,29,30] securement,[15,29,30,32] prompting removal of unnecessary catheters,[21,25,29,30] improving incontinence care,[15,21,23,25] bladder scanners,[37,38] catheter changes,[35]and comparing alternatives (condom catheter or intermittent straight catheter) to use of an indwelling catheter.[36,38] None focused on improving aseptic insertion. General infection control practices studied included improving hand hygiene,[20-22,29-31,33,34] improving antibiotic use,[15,20,21,28,34] initiation of infection control programs,[20,21,28] interventions to improve identification of UTIs/CAUTIs using infection symptom/sign criteria,[15,20,21,34] infection surveillance as an intervention,[28-30,33,34] and barrier precautions,[33,34] including

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TABLE 2. Summary of Outcomes from Included Studies

First Author, Year	UTI, CAUTI, Bacteriuria measures	Comparison Group	Intervention	Urinary Catheter Use Measures	Comparison Group	Intervention
Studies including participants who could be with or without urinary catheterization (ie, not limited to catheterized patients only)						
Ahlbrecht, 1999[20]	Overall UTI rate/1000 resident days	1.18 (CI: 0.36, 2.01)	1.14 (CI: 0.94, 1.34), P = 0.65	None reported		
	UTIs in nonambulatory females without indwelling catheters/1000 resident days	2.40 (CI: 1.96, 2.84)	3.06 (CI: 2.19, 3.93), P = 0.05	Not applicable		
Brownhill[a], 2013[15]	Mean UTI/month	55 UTIs	18.8 UTIs	Not reported		
	Mean CAUTI/month	18.3 CAUTIs	4.3 CAUTIs	Not reported		
Cools, 1988[21]	UTIs treated with antimicrobials (includes with and without catheters)	0.49 (256 UTIs in 515 residents) in year 1	0.125 (66 UTIs in 527 residents in year 6	Prevalence (%) of indwelling catheters	Year 1=21% (109/515)	Year 6=10% (52/527)
Fendler, 2002[22]	CAUTIs per 1000 patient-days, by symptomatic infection, 1991 McGeer criteria[42]	0.77 (133 CAUTIs per 172,897 patient-days)	0.63 (51 CAUTIs per 81,036 patient-days)	Not reported		
Klay, 2005[23]	Number of UTIs (not defined further by symptom or catheter-association)	31 UTIs	6 UTIs	Not reported		
Lin, 2013[24]	Asymptomatic bacteriuria in patients without indwelling catheters	Control group Baseline: 16.7% (n=5 of 30) Follow-up: 10% (n=3 of 30)	Intervention group Baseline: 38.6% (n=17 of 44) Post-intervention: 22.7% (n=10 of 44)	Not reported		
		No significant bacteriuria for either group				
McConnell, 1984[25]	Number of UTIs (unclear if restricted to symptomatic; population seems to include both those with and without catheters)	Monthly rates of 3-9 UTIs in months June-November 1982 (before full implementation in December 1982)	Monthly rates of 1-3 UTI in December-June 1982 (after December 1982 full implementation)	Not reported		
Mentes, 2003[26]	Hydration-linked event of UTI diagnosed by a provider (unclear if symptoms, catheter use, or other criteria), proceeded by urine specific gravity of ≥ 1.010 and decreased fluid intake	1 UTI (4.1% of 24 control patients)	0 UTI (0% of 25 treatment patients)	Not reported		
Miller, 2014[27]	Percentage of residents with UTI in last 30 days reported in Minimum Data Set:	531 NHs in bottom 3 quartiles of culture change composite score Baseline period: 8.4%±5.6 (SD) Follow-up period: 8.9%±5.4 (SD)	207 NHs in top quartile of culture change composite score Baseline period: 8.8%±4.9 (SD) Follow-up period: 8.6%±5.1 (SD)	Not reported		
		Coefficient +0.72 (SE, 0.28), meaning higher UTI rates, P = 0.01	Coefficient -0.06 (SE, 0.54), P = 0.92			
Stuart, 2015[28]	UTI rates form surveillance data using McGeer's criteria	Data not provided, but text indicates surveillance infection rates surveillance data remained stable over the 2 data collection periods		Not reported		
Van Gaal, 2011[29,30]	Symptomatic UTI confirmed by physician, reported as incidence rate per patient per week	Baseline period: n=28 UTIs for 127 patients, occurring at rate of 0.03 per patient per week Follow-up period: n=57 UTIs for 196 patients, occurring at rate of 0.02 per patient per week	Baseline period: n=23 UTIs for 114 patients, occurring at rate of 0.03 per patient per week Follow-up period: n=58 UTIs for 196 patients, occurring at rate of 0.02 per patient per week	Patients with indwelling catheters with a correct indication (%)	Usual care Baseline: 6% Follow-up: 34%	Intervention Baseline: 34% Follow-up: 32%
		Overall UTI outcome for this study, reported as ratio of UTIs in intervention versus usual care group: 0.85 with 96% CI: 0.43-1.67				

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TABLE 2. Summary of Outcomes from Included Studies (continued)

First Author, Year	UTI, CAUTI, Bacteriuria measures	Comparison Group	Intervention	Urinary Catheter Use Measures	Comparison Group	Intervention
Yeung, 2011[31]	UTIs requiring hospitalization, unclear if with or without catheters	Baseline period: 3 UTIs per 32,726 resident-days, calculated as 0.09 per 1000 resident-days Follow-up period: 22 UTIs per 81,177 resident-days, calculated as 0.27 per 1000 resident-days, $P = 0.06$	Baseline period: 6 UTIs per 21,862 resident-days, calculated as 0.27 per 1000 resident-days Follow-up period: 8 UTIs per 50,441 resident-days, calculated as 0.16 per 1000 resident-days), $P = 0.30$	Not reported		
Studies including only catheterized participants or in settings where very high urinary catheterization rates expected						
Darouiche, 2006[32]	Number of symptomatic CAUTIs in patients with Foley or suprapubic catheters	14 CAUTIs (24.1% of 58 patients followed)	8 CAUTIs (13.3% of 60 patients followed). RR=0.55, 95% CI: 0.25-1.22; $P = 0.16$	Not reported		
	Symptomatic CAUTI rate as CAUTIs per 1000 device days	4.9 CAUTI per 1000 device days	2.7 CAUTI per 1000 device days, $P = 0.16$ but study not powered to detect significant change	Not reported		
Evans, 2013[33]	MRSA hospital-associated UTIs	Actual Ns and rates were not provided in report	Quarterly UTI rates declined by 33% ($P = 0.07$)	Not reported		
Mody, 2015[34]	Clinically-defined (symptomatic) first new CAUTIs per 1000 device-days	10.0 CAUTIs per 1000 device-days	5.2 CAUTIs per 1000 device-days (HR, 0.54; (95% CI: 0.30, 0.97), $P = 0.04$[b]	Not reported		
	Clinically-defined (symptomatic) all new CAUTIs (includes recurrent) per 1000 device-days	9.2 CAUTIs per 1000 device-days	5.9 CAUTIs per 1000 device-days (HR, 0.69 (95% CI: 0.49, 0.99), $P = 0.045$[b]	Not reported		
Priefer, 1982[35]	Number (%) of patients with symptomatic CAUTI in patients with indwelling catheters	Control group: 6 of 7 (83%) men	Experimental 3 of 10 (30%) men	Not reported		
	Number of symptomatic CAUTIs per patient in 6 months in indwelling catheter patients	Control group: 1.0 ±0.6	Experimental: 0.4 ±0.7 $P > 0.05$	Not reported		
Saint, 2006[36]	Number with bacteriuria (≥10^3 CFUs per mL of single/predominant species)	Indwelling catheters: n=17 (SE, 41.5)	Condom catheter group: n=13 (SE, 38.2)	Not reported		
	Bacteriuria per 1000 patient-days (95% CI)	Indwelling catheters: 111/1000 patient-days, 95% CI (69-178)	Condom catheter group: 61/1000 patient-days with 95% CI (35-104), $P = 0.11$	Not reported		
	Composite outcome: number with bacteriuria *or* CAUTI (defined by bacteriuria and ≥ 1 UTI sign/symptom) *or* death	Indwelling catheters: n=20 (48.8%)	Condom catheter group: n=15 (44.1%)	Not reported		
		HR, 2.11 (95% CI, 1.03-4.31), $P = 0.04$ comparing this event in those with indwelling vs. condom catheters				
	Composite outcome: combined event (bacteriuria or CAUTI *or* death) per 1000 patient-days	Indwelling catheters: 131 per 1000 patient-days with 95% CI (85-203)	Condom catheter group: 70 per 1,000 patient-days with 95% CI (42-116), $P = 0.07$	Not reported		
Suardi, 2001[37]	Not reported			Number of intermittent catheterizations and indwelling catheters used	No Ns reported	No Ns reported. By text, reduced indwelling catheters, $P < 0.001$[b]
Tang, 2006[38]	Symptomatic CAUTI by day 14	Indwelling catheter group: 0	Intermittent catheter group: 1. $P = 0.400$	Days to become catheter-free	Indwelling catheters: 9.2±4.0 days	Intermittent catheters: 8.6±3.3 days $P = 0.609$
	Bacteriuria by day 14	Indwelling catheter group: 21 of 34 (61.8%) P=0.888	Intermittent catheter group: 14 of 22 (63.6%)	Number patients catheter-free by day 14 with postvoid residual <150 mL	Indwelling catheters: 27 of 39 (69.2%),	Intermittent catheters: 16 of 27 (59.3%) $P = 0.403$

[a]Study author provided outcome data not in published article.

[b]Result statistically significant, $P < .05$.

NOTE: Abbreviations: CAUTI: catheter-associated urinary tract infection; CFU, colony-forming units; CI, 95% confidence intervals; UTI, urinary tract infection not specified as catheter-associated; HR, hazard ratio; MRSA, methicillin-resistant Staphylococcus aureus; NH, nursing home; SD, standard deviation. SE, standard error.

TABLE 3. Comprehensive List of Interventions Considered for Prevention of UTI and CAUTI

This table includes a comprehensive list of potential interventions that have been considered for prevention of UTI or CAUTI (including those in acute and long-term settings), as summarized from this evidence report, and prior comprehensive narrative[43-57] or systematic reviews.[11,58-68] Blue-shaded cells describe interventions that are not recommended based on available evidence or rationale. Nonshaded cells describe interventions that have some evidence of benefit (not always from controlled-intervention studies) for certain populations and settings.

Interventions	General Summary of Available Evidence and Recommendations Provided
Interventions for Patients Regardless of Urinary Catheter Status	
Hand hygiene	Interventions to improve hand hygiene have been studied as single interventions[22,31] and part of bundles[12,21,33,34] for prevention of UTI and CAUTI in LTC settings with decreased (without statistical significance) CAUTI rates[22] with no clear benefit in UTIs require hospitalization[31] marked decrease in MRSA UTIs[33] and CAUTIs[34] in a multi-intervention studies[33,34] including contact precaution interventions
Encourage fluid intake/hydration to reduce infection	Studied as single interventions[24,26] and part of bundles[25] for the LTC setting with no significant benefits demonstrated regarding infection prevention
Improve general patient hygiene to reduce infection	Studied only as part of CAUTI bundles in the LTC setting including 1 with marked decreases in unspecified CAUTIs without statistical significance noted[12] and 1[20] without improvement in symptomatic UTIs
Cranberry product as prophylaxis	The use of cranberry-containing products (eg, juice, capsules/tablets, extracts) has been assessed in recent systematic reviews and meta-analyses,[58,59,69] evaluating a total of 14 heterogeneous studies in multiple settings (outpatient, hospital, LTC, spinal cord injury). Both recent meta-analyses[58,59] demonstrated similar nonsignificant pooled risk ratios for symptomatic UTIs, although 1 meta-analysis found a significant protection for subgroups such as women with recurrent UTIs[59] that was seen in the other meta-analysis.[58] Of note, individual studies in the LTC setting have reported mixed results on bacteriuria outcomes[70-72] and UTIs.[73-75] Cranberry studies in spinal cord injury patients[76,77] did not reduce either bacteriuria or UTI outcomes. A very recent abstract[78] regarding a double-blind placebo-controlled RCT published regarding effectiveness of twice daily cranberry capsules in LTC suggested reduced rates of clinically defined UTIs with treatment effect of 0.79 (95% CI, 0.60-1.03) among patients at high risk for UTI (long-term catheterization, diabetes, ≥1 UTI in prior year) and 0.83 (95% CI, 0.60-1.16) among patients at low risk for UTI, but not likely to be cost effective.[79] In contrast, another very recently published double-blinded placebo-controlled RCT regarding the effectiveness of 2 oral cranberry capsules once daily resulted in no significant difference in the presence of bacteriuria plus pyruria over 1 year among older women residing in nursing homes.[80]
Vitamin/mineral supplement as UTI prophylaxis	Ineffective in RCT[81] for prevention of symptomatic UTIs per 1000 resident-days in LTC setting
Treatment of atrophic vaginitis as UTI prophylaxis	Treatment of atrophic vaginitis with topical vaginal estrogens in postmenopausal women with recurrent UTIs (in outpatient setting) has been supported by RCTs (single blind[82] and double-blind[52] and by a respective chart review of a case series[83] of female LTC nursing home residents with recurrent UTI.
Interventions to improve management of urinary incontinence	Studied as educational strategies[21,23,25,29,30,38,39] and protocols regarding incontinence care for staff and residents/family, in addition to interventions of incontinence specialists,[23,39] providing individualized treatment plans to LTC residents, which can include a variety of interventions such as pelvic floor exercises, medical treatment for specific types of incontinence including avoidance of exacerbating medication and treatment of atrophic vaginitis
Implementation of effective infection control program	Infection control program implementation often includes several interventions including hand-hygiene programs, and surveillance of nosocomial infections including UTI with the potential as feedback[20] to motivate reductions in unnecessary catheter use and improved catheter care. Such interventions have been studied in the LTC setting in studies[20,21] including other specific interventions targeting CAUTIs (including infection control "walk rounds" for CAUTI detection, fed back daily to nurses).[20]
Interventions to Reduce Unnecessary Indwelling Urinary Catheter Placement: Disrupting Lifecycle Stages 1 and 4 of Urinary Catheters	
Education regarding the hazards of urinary catheters	Educational interventions aiming to improve staff knowledge of CAUTI and urinary catheter risks are common components in multi-intervention studies implemented in both acute and LTC settings. Of note, in the LTC setting, educational strategies studied have included modules specific for all healthcare workers (unlicensed and licensed) who care for catheters with separate modules for nurses who insert catheters, with multiple formats including online,[84,85] small-group teaching sessions and case reviews, and education of patients/residents[13,25,29] and families.[13,29]
Education and/or policies regarding appropriate indications for indwelling catheters	Education and policies regarding appropriate (and inappropriate) indications for indwelling catheters have been common in the acute care setting,[11] often as part of a bundle of CAUTI preventive strategies, implementing the HICPAC list[86] of appropriate indications. These lists have also been implemented in the LTC setting[13,39] with either modifications of lists from acute care or LTC.[87]
Requiring physician order with appropriate indication before placing indwelling catheters	Requiring physician orders for catheter placement has been studied in both acute care[11] and LTC settings[13,84]
Requiring documentation of staff who insert the catheters with reason for catheter placement	Requiring nurses to document insertion with indication has been an intervention employed specifically in the emergency setting[84] where catheters were placed without electronic orders and in settings where nurses are empowered to remove catheters by criteria
Education and supplies for alternatives to indwelling catheters such as external catheters, ISCs, and noncatheter strategies for managing incontinence	Facilitating use of alternatives to indwelling catheters is recommended[86] and supported by either lower UTI or other complication rates in patients treated with external catheters,[36] intermittent catheters, and noncatheter[88] strategies compared to indwelling Foley catheters
Urinary retention protocols for ISC and/or bladder scanner use before indwelling catheters requested	Bladder scanners have been used in acute care (postprocedure and floor settings) and in the rehabilitation setting[37,38] to confirm sufficient urinary retention prior to catheterization, to reduce the number of catheterizations.
Interventions to Improve Catheter Insertion Technique: Disrupting Lifecycle Stage 1 of Urinary Catheters	
Education for aseptic insertion of indwelling catheters	Although not confirmed as effective by limited evidence,[89] aseptic (as opposed to clean non-sterile) insertion of indwelling catheters is the accepted and recommended[86,90] practice in all settings. Nurse education regarding urinary catheter avoidance, maintenance, insertion, and removal that included one-on-one teaching is preferred, and resulted in higher adherence to CAUTI prevention bundle elements over online education alone.[91]
Hands-on training/competency assessments regarding aseptic indwelling catheter insertion	Catheter placement by "only properly trained persons" using aseptic technique is recommended.[86] The use of competency assessments in LTC has been studied[12,13,85] in CAUTI bundles, although the individual impact of competency training interventions cannot be assessed from available studies. The CDC evidence-based guideline[86] recommends that healthcare personnel and others who care for catheters be given periodic in-service training regarding techniques and procedures for catheter insertion, maintenance, and removal.
Options regarding intermittent catheterization	Clean vs. sterile, and single-use vs. multi-use intermittent catheterization has also been studied including several studies in the LTC and rehabilitation settings,[92-95] with a systematic review[60] indicating no evidence that UTI rates are impacted by these options, in agreement with evidence-based guidelines[86,90] indicating that clean (non-sterile) ISC is acceptable for patients requiring chronic ISC, with guidelines still recommending aseptic insertion for indwelling catheters, although the limited evidence[89] regarding this is not convincing.

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TABLE 3. Comprehensive List of Interventions Considered for Prevention of UTI and CAUTI (continued)

Interventions	General Summary of Available Evidence and Recommendations Provided
Standardizing catheter-placement supplies/kit	Catheter kit standardization (aiming to standardize catheter placement by making the necessary supplies readily available) is occurring in some acute care settings similar to prior "kit" interventions for prevention of blood-stream infections. Some LTC setting studies[13] mention interventions regarding selection of catheter products but have not been specific regarding use of a catheter kit as opposed to individual catheter products.
Interventions to Improve Catheter Insertion Technique: Disrupting Lifecycle Stage 1 of Urinary Catheters	
Type of catheterization	Comparing different types of catheterization (indwelling catheters vs. ISCs vs. external catheters) has also been the subject of systematic reviews. One[62] systematic review had zero studies meeting the inclusion criteria. Another[66] systematic review focused on suprapubic catheters, with the available evidence of 14 studies (no RCTs, 1 prospective nonrandomized study with a comparator, 8 retrospective reviews with comparators, a case series, and qualitative/descriptive assessments of quality of life) reports no evidence of differences between symptomatic UTI outcomes between suprapubic and urethral catheters, although the evidence is limited by varied UTI definitions applied for outcomes. However, a Cochrane systematic review[96] comparing short-term (<14 days) of indwelling urethral urinary catheters to suprapubic urinary catheters found that groups with indwelling urinary catheters had more cases of bacteriuria (RR 2.6, 95% CI, 2.12, 3.18) and significantly more patient discomfort (RR 2.98; 95% CI, 2.31, 3.85). Evidence-based guidelines[86] recommend ISC use is preferable to indwelling suprapubic or urethral catheters for bladder-emptying dysfunction, based on decreased rates of symptomatic UTIs and unspecified UTIs in select patient populations. Despite some evidence of lower CAUTI rates for external catheters and ISC compared to indwelling catheters, no catheter is preferable because of increased rates[97,98] of symptomatic UTI even with nonindwelling catheters by observational studies.
Catheter coating/materials	Different options in catheter coatings (such as hydrophilic-coated, antiseptic or antibiotic-impregnated) and materials (latex, PVC, silicone) have been studied. Systematic reviews suggest either insufficient evidence for recommendation[99] or no evidence that UTI rates are impacted by these options; the CDC[86] targeted systematic review suggesting antimicrobial/aseptic catheters may be useful if CAUTI rates are not decreasing with other strategies. A more recent RCT in the acute care setting demonstrated no benefit of antimicrobial catheters.[100] Although prior evidence-based guidelines were mixed[86,90] regarding routine use of hydrophilic catheters for ISC, a 2013 systematic review and meta-analysis[61] of hydrophilic catheters in the spinal cord injury population indicate these may be preferable (compared to standard nonhydrophilic catheters) for intermittent straight catheterization, with a significantly lower incidence of symptomatic or treated UTIs (OR, 0.36; 95% CI, 24%-54%; $P < 0.001$).
Catheter tip options	Different options in catheter tip configurations for catheters used for intermittent catheterization (such as straight, coude, olive tip, or introducer-tip) are discussed in narrative reviews citing potential benefits for certain patient populations (such as using coude catheters for men with enlarged prostates). These types of recommendations may be valid clinically and are choices sometimes recommended by urologists in cases of difficult placement.[56] There is insufficient evidence to recommend specific catheter tips as a general CAUTI bundle component for the average patient.
Catheter size	The smallest bore catheter possible with consistent good drainage is recommended to avoid black neck and urethral mucosa trauma.[54,86]
Catheter length	Narrative reviews suggest than the optimal catheter length varies by gender[54] (45 cm, males; 25 cm, females) to avoid kinking. Specific recommendations regarding catheter length have not been provided by recent evidence-based reviews, although keeping the catheter free from kinking to maintain unobstructed urine flow is recommended.[86,90]
"Closed" drainage systems	Evidence-based guidelines[86,90] recommend the use of closed catheter drainage systems to reduce CAUTI in patients with indwelling catheters. Closed drainage systems for intermittent straight catheters also exist but with limited evidence[56] regarding benefit.
Catheter securing devices	Properly securing indwelling catheters after insertion is recommended to decrease movement and urethral trauma and has been studied as part of a bundle[85] in the rehabilitation setting. The use of a specific device (StatLock) was studied in the spinal cord injury acute care setting with a marked reduction (without meeting statistical significance) in symptomatic CAUTI rates;[32] the implications of this study have been mixed with some interpreting it as evidence for supporting use of this type of catheter-securing device, and other[86] reviews interpreting as not evidence for using these devices given no significant difference in CAUTI or meatal erosion.
Maintenance/Care of Patients with Catheters: Disrupting Lifecycle Stage 2 of Urinary Catheters	
Handwashing, gloving before and after catheter/bag care	Hand hygiene is recommended[86] immediately before and after insertion or any manipulation of the urinary catheter or site. Gloves should be worn during any manipulation of catheterized patients or when providing intimate care. Gown use should be considered during catheter insertions, manipulation, and when providing assistance during activities of daily living. These strategies are useful regardless of a resident's colonization status with multidrug resistant organisms.
Keeping drainage bag below bladder	Keeping the collecting bag below the level of the bladder at all times without placement of the bag on the floor is recommended by evidence-based guidelines.[86]
Routine perineal cleaning strategies with antiseptics	Evidence-based guidelines[86,90,101] recommend against cleaning the periurethral area with antiseptics to prevent CAUTI while the catheter is in place. Routine hygiene (cleansing of the meatal surface during daily bathing) is appropriate.[90]
Irrigations, washouts, and instillations	The practice of irrigating or washing out long-term indwelling urinary catheters has also been assessed by systematic reviews[65,102] including reviews of various solutions (eg, saline, acidic solutions, antiseptic, and antibiotic solutions) have summarized 5 studies in multiple settings that were noted to be of poor quality and also did not appear to support these interventions as effective at either reductions of symptomatic CAUTIs or time to requiring first catheter change. Our own systematic search strategy identified several studies involving these interventions that either had been evaluated for the previously published systematic reviews (as included[103,104] or excluded[105] studies). Washout and irrigation strategies have also been assessed at length by a recent CDC-targeted systematic review,[86] with agreement that bladder irrigation and catheter drainage bag instillations are not recommended, given no differences in symptomatic UTI and mixed results in bacteriuria outcomes.
Catheter replacement issues	Catheter replacement at routine, fixed intervals is not recommended by evidence-based guidelines[86] and did not decrease UTIs in the study reviewed in detail in this systematic review.[35] A recent integrative review on catheter change intervals concluded there was insufficient evidence to support or refute the common practice of routine catheter changes but is a pre-emptive strategy employed in those who encrust and develop recurrent blockage.[106]
Avoid equipment sharing between catheterized patients	This has been recommended in narrative reviews[45,107] and is reasonable and recommended by the CDC guideline[86] with regard to not sharing catheter-care supplies (such as devices used to empty catheter bags).
Spatial separation of catheterized patients	Spatial separation has been recommended by a case-control study,[108] but further research is needed to assess the benefit of spatial separation of catheterized patients.[86]

Continued on page 365

TABLE 3. Comprehensive List of Interventions Considered for Prevention of UTI and CAUTI (continued)

Interventions	General Summary of Available Evidence and Recommendations Provided
Maintenance/Care of Patients with Catheters: Disrupting Lifecycle Stage 2 of Urinary Catheters	
Prophylaxis with systematic antimicrobials	The use of antimicrobial prophylaxis for chronically catheterized patients studied in several studies[109-112] yielded by our search strategy has also been reviewed in a recent systematic review[68] (of 8 studies, including indwelling catheters and ISCs) and systematic review and meta-analysis[67] (of 15 studies involving ISCs) systematic reviews[67,68] and meta-analyses[67] with no benefit seen in patients with either chronic catheters or ISCs (with increased resistance[67] suggested in ISC patients), in agreement with a recent CDC[86] targeted systematic review. Our search did reveal a very recent study[64] supporting the use of antimicrobial prophylaxis when short-term catheters are removed in the acute care setting; however, other studies indicate that prophylactic antimicrobials are not routinely indicated for changes of chronic catheters due to little morbidity[45,113,114] reported with chronic catheter changes.
Other systemic chemoprophylaxis	The evidence for methenamine IN preventing CAUTI is limited for use in both short-term catheterizations (studied only for postoperative gynecologic surgery) and long-term catheterizations, and not recommended for routine use for patients with long-term intermittent or long-term indwelling urethral or suprapubic catheterization according to evidence-based guidelines.[86,90]
Bacterial interference interventions	Novel interventions are being studied[115] regarding the feasibility and potential benefit of "bacterial interference" interventions involving urinary colonization with benign bacteria, with the goal to reduce symptomatic infections by pathologic bacteria.
Prompting Removal of Unnecessary Catheters: Disrupting Lifecycle Stage 3 of Urinary Catheters	
Trial removal of indwelling catheters present at admission to LTC setting	This practice has been studied as a bundle component[21,25,39] in LTC settings, and functions as a type of stop-order by prompting a trial removal of all indwelling catheters upon admission to LTC setting. This type of intervention may function similarly to stop-orders studied in the acute care setting. Studies reporting this type of intervention are advised to assess and report potential adverse events to patients, similar to acute care interventions using reminders and stop-orders.[11]
Urinary catheter reminders, reminding staff that patient/resident has a catheter to consider removing Urinary catheter stop-orders, requiring removal of catheter unless specific clinical criteria are met	The use of reminders and/or stop-orders has been demonstrated by a recent systematic review and meta-analysis[11] focused on the acute care setting to reduce CAUTIs per 1000 catheter-days by more than 50%; these studies often included reminders/stop-orders as part of a CAUTI prevention bundle. Reminder types included use of daily checklists, electronic reminders, and the use of catheter patrols. Similar interventions have also been implemented in a few LTC studies including the use of catheter audit tools,[39] daily assessment for continued catheter need,[13] electronic removal reminder systems[14] with some studies reporting decreased infections or catheter use, although most studies were underpowered to detect statistical significance of these interventions in the LTC setting.

NOTE: Abbreviations: CAUTI, catheter-associated urinary tract infection; CDC, Centers for Disease Control and Prevention; CI, confidence interval; HICPAC, Healthcare Infection Control Practices Advisory Committee; ISC, intermittent straight catheterization; LTC, long-term care; OR, odds ratio; PVC, polyvinyl chloride; RCT, randomized controlled trial; RR, relative risk; UTI, urinary tract infection.

preemptive precautions for catheterized patients.[34] Hydration was assessed in 3 studies.[24-26]

Outcomes of Included Studies

Table 2 describes the studies' outcomes reported for UTI, CAUTI, or bacteriuria.[15,20-38] The outcome definitions of UTI and CAUTI varied widely. Only 2 studies[22,39] reported UTI outcomes using definitions specific for nursing home settings such as McGeer's criteria[40] a detailed review and comparison of published CAUTI definitions used clinically and for surveillance in nursing homes is provided in Supplemental Table 3. Two studies reported symptomatic CAUTIs per 1000 catheter-days.[32,34] Another study[22] reported symptomatic CAUTIs per 1000 resident-days. Three reported symptomatic CAUTIs as counts.[35,38] Saint et al[36] reported CAUTIs as part of a combined outcome (ie, bacteriuria, CAUTI, or death).

The 19 studies (Table 2) reported 12 UTI outcomes,[15,20,21,23,25-31,33] 9 CAUTI outcomes,[15,22,32,34,35,38] 4 bacteriuria outcomes,[24,36,38] and 5 catheter use outcomes.[21,29,30,37,38] Five studies showed CAUTI reduction[15,22,32,34,35] (1 significantly[34]); 9 studies showed UTI reduction[13,18,19,21,23-25,27,28,31] (none significantly); 2 studies showed bacteriuria reduction (none significantly). One study[36] reported 2 composite outcomes including bacteriuria or CAUTI or death, with statistically significant improvement reported for 1 composite measure. Four studies reported catheter use, with all showing reduced catheter use in the intervention group; however, only 1 achieved statistically significant reduction.[37]

Synthesis of Systematic Review Results

Overall, many studies reported decreases in UTI, CAUTI, and urinary catheter use measures but without statistical significance, with many studies likely underpowered for our outcomes of interest. Often, the outcomes of interest in this systematic review were not the main outcome for which the study was designed and originally powered. The interventions studied included several currently implemented as part of CAUTI bundles in the acute care setting, such as improving catheter use, and care and infection control strategies. Other included interventions target common challenges specific to the nursing home setting such as removing indwelling catheters upon admission to the nursing home from an acute-care facility[21,25] and applying interventions to address incontinence by either general strategies[21,23,25,30,38] or the use of an incontinence specialist[23] to provide individual treatment plans. The only intervention that demonstrated a statistically significant reduction in CAUTI in chronically catheterized patients employed a comprehensive program to improve antimicrobial use, hand hygiene (including hand hygiene and gloves for catheter care), and preemptive precautions for patients with devices, along with promotion of standardized CAUTI definitions and active multidrug resistant organism surveillance.[34]

Narrative Review Results

Table 3 includes a comprehensive list of potential interventions that have been considered for prevention of UTI or CAUTI (including those in acute care and nursing home

settings), as summarized from this systematic review and prior narrative or systematic reviews.[43-115]

DISCUSSION

We performed a broad systematic review of strategies to decrease UTI, CAUTI, and urinary catheter use that may be helpful in nursing homes. While many studies reported decreased UTI, CAUTI, or urinary catheter use measures, few demonstrated statistically significant reductions perhaps because many were underpowered to assess statistical significance. Pooled analyses were not feasible to provide the expected impact of these interventions in the nursing home setting.

This review confirms that bundles of interventions for prevention of CAUTI have been implemented with some evidence of success in nursing home settings, with several components in common with those implemented in the acute care setting, such as hand hygiene and strategies to reduce and improve catheter use.[41] Some studies focused on issues more common in nursing homes such as chronic catheterization and incontinence. A nursing home CAUTI bundle should be designed with the resources and challenges present in the nursing home environment in mind, and with recognition that, although the number of patients with catheters is less than in acute care, there will be more patients with chronic catheterization needs and incontinence.

Although catheter utilization in nursing homes is low, further reductions in catheter days and CAUTIs can be achieved. Catheter removal reminders and stop orders have demonstrated a greater than 50% reduction in CAUTIs in acute care settings;[11] an example of a stop-order intervention in nursing homes is trial removal of indwelling catheters present at facility admission without clear urologic need present at the time of admission.[25] Nursing home interventions to avoid catheter placement should include incontinence programs, discussion of alternatives to indwelling urinary catheters with patients, families, and frontline personnel, and urinary retention protocols. Programs to reduce CAUTI should include education to improve aseptic insertion, and to maintain awareness and proper care of catheters in place by regular assessment of catheter necessity, securement, hand hygiene, and preemptive barrier precautions for catheterized patients. Interventions that focus on improving appropriate use of urine tests and antibiotics to treat UTIs can also significantly affect the rates of reported symptomatic CAUTIs, with the potential to decrease unnecessary antibiotic use.[20,21]

The main limitation of this review is that many studies provided little information about their intervention and definition of outcomes. The strength of this review is the detailed and broad search strategy applied with generous inclusion of interventions and outcomes to highlight the available evidence and details of interventions that have been studied and implemented.

CONCLUSION

This review synthesizes the current state of evidence and proposes strategies to reduce UTIs in nursing homes. Interventions that motivate catheter avoidance and catheter removal to prevent CAUTI in acute care[11] and nursing home settings are supported by the strongest available evidence, although the strength of that evidence is less in the nursing home setting. Limitations notwithstanding, interventions such as incontinence care planning and hydration programs can reduce UTI in this population and is important for overall wellbeing.

Acknowledgments

The authors appreciate the guidance that Vineet Chopra MD, MSc, provided regarding options for methodological quality assessment tools, and the assistance of Mary Rogers PhD, MS, in interpreting the published Downs and Black Quality Index items, which informed our modification of this tool for application in this study. The authors appreciate, also, the feedback provided by the Agency for Healthcare Research and Quality (AHRQ) Content and Materials Development Committee for the AHRQ Safety Program for Long-Term Care: Preventing CAUTI and other Healthcare-associated Infections.

Disclosures: Agency for Healthcare Research and Quality (AHRQ) contract #HHSA290201000025I provided funding for this study, which was developed in response to AHRQ Task Order #8 for ACTION II RFTO 26 CUSP for CAUTI in LTC. AHRQ developed the details of the task and provided comments on a draft report, which informed the report submitted to AHRQ in December 2013, used to inform the interventions for a national collaborative (http://www.hret.org/quality/projects/long-term-care-cauti.shtml). Dr. Meddings's effort on this project was funded by concurrent effort from her AHRQ (K08 HS19767). Dr. Saint's and Dr. Krein's effort on this project was funded by concurrent effort from the Veterans Affairs National Center for Patient Safety, Ann Arbor Patient Safety Center of Inquiry. Dr. Meddings's other research is funded by AHRQ (2R01HS018334-04), the NIH-LRP program, the VA National Center for Patient Safety, and the VA Ann Arbor Patient Safety Center of Inquiry. Dr. Krein's other research is funded by a VA Health Services Research and Development Award (RCS 11-222). Dr. Mody's other research is funded by VA Healthcare System Geriatric Research Clinical Care Center (GRECC), NIA-Pepper Center, NIA (R01AG032298, R01AG041780, K24AG050685-01). Dr. Saint has received fees for serving on advisory boards for Doximity and Jvion. All other authors report no financial conflicts of interest. The findings and conclusions in this report are those of the authors and do not necessarily represent those of the sponsor, the Agency for Healthcare Research and Quality, or the U.S. Department of Veterans Affairs. These analyses were presented in part as a poster presentation at the ID Week Annual Meeting on October 10, 2014 in Philadelphia, PA.

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Inpatient Management of Opioid Use Disorder: A Review for Hospitalists

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The United States is experiencing an epidemic of nonmedical opioid use and opioid overdose-related deaths. As a result, there have been a number of public health interventions aimed at addressing this epidemic. However, these interventions fail to address care of individuals with opioid use disorder during hospitalizations and, therefore, miss a key opportunity for intervention. The role of hospitalists in managing hospitalized patients with opioid use disorder is not established. In this review, we discuss the inpatient management of individuals with opioid use disorder, including the treatment of withdrawal, benefits of medication-assisted treatment, and application of harm-reduction strategies. *Journal of Hospital Medicine* 2017;12:369-374. © 2017 Society of Hospital Medicine

The United States is experiencing an epidemic of nonmedical opioid use. A concerted effort to better address pain increased the provision of prescription narcotics in the late 1990s and early 2000s.[1] Since then, there has been significant growth of opioid use and a corresponding increase in overdose-related deaths.[1-3] Public health officials have responded with initiatives to secure the opioid supply and improve outpatient treatment resources. However, the role of hospitalists in addressing opioid use disorder (OUD) is not well established. The inpatient needs for these individuals are complex and require a collaborative approach with input from outpatient clinicians, inpatient clinicians, addiction specialists, social workers, and case managers. Hospitals are often under-resourced to provide such comprehensive services. This frequently results in the hospitalist bearing significant responsibility for inpatient addiction management despite often insufficient addiction education or experience.[4,5]

Therefore, there is a need for hospitalists to become leaders in the inpatient management of OUD. In this review, we will discuss the hospitalist's role in the inpatient management of individuals with OUD.

INPATIENT MANAGEMENT OF OPIOID USE DISORDER

Opioid use disorder is a medical illness resulting from neurobiological changes that cause drug tolerance, dependence, and cravings.[6] It should be considered a treatable chronic medical condition, comparable to hypertension or diabetes,[7] which requires a multifaceted treatment approach, including psychosocial, educational, and medical interventions.

Psychosocial Interventions

Individuals with OUD often have complicated social issues including stigmatization, involvement in the criminal justice system, unemployment, and homelessness,[5,8-10] in addition to frequent comorbid mental health issues.[11,12] Failure to address social or mental health barriers may lead to a lack of engagement in the treatment of OUD. The long-term management of OUD should involve outpatient psychotherapy and may include individual or group therapy, behavioral therapy, family counseling, or support groups.[13] In the inpatient setting, hospitalists should use a collaborative approach to address psychosocial barriers. The authors recommend social work and case management consultations and consideration of psychiatric consultation when appropriate.

Management of Opioid Withdrawal

The prompt recognition and management of withdrawal is essential in hospitalized patients with OUD. The signs and symptoms of withdrawal can be evaluated by using the Clinical Opiate Withdrawal Scale or the Clinical Institute Narcotics Assessment, and may include lacrimation, rhinorrhea, diaphoresis, yawning, restlessness, insomnia, piloerection, myalgia, arthralgia, abdominal pain, nausea, vomiting, and diarrhea.[4] Individuals using short-acting opioids, such as oxycodone or heroin, may develop withdrawal symptoms 8 to 12 hours after cessation of the opioid. Symptoms often peak on days 1 to 3 and can last for up to 10 days.[14] Individuals taking long-acting opioids, such as methadone, may experience withdrawal symptoms for up to 21 days.[14]

While the goal of withdrawal treatment is to reduce the uncomfortable symptoms of withdrawal, there may be additional benefits. Around 16% of people who inject drugs will misuse drugs during their hospitalization, and 25% to

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Received: January 28, 2016; **Revised**: August 30, 2016; **Accepted**: September 25, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2731

TABLE 1. Treatment Options for Opioid Withdrawal[4,17-20]

Opioid substitution treatment
Methadone
• Initial dose: 10 to 20 mg of oral, or 10 mg of intramuscular, methadone
• Reassess and re-dose: reassess the patient every 2 to 4 hours; if the patient has withdrawal symptoms, give an additional 10 mg of oral methadone; if the symptoms are controlled or the patient is somnolent, do not give additional doses; the maximum first day dose of oral methadone is 40 mg.
• Taper: reduce the daily dose by 10% to 20% daily; the taper duration will last approximately 10 to 14 days.
• Monitoring: EKG before and after methadone administration
• Selected adverse effects: sedation, constipation, prolonged QTc, torsades de pointes
Buprenorphine[a]
• Initial dose: 4 mg of sublingual buprenorphine
• Reassess and re-dose: reassess the patient in 2 to 4 hours; if the patient has withdrawal symptoms, give an additional 4 mg of sublingual buprenorphine; if the symptoms are controlled or the patient is somnolent, do not give additional doses; the day 1 maximum dose is 8 mg of sublingual buprenorphine; uptitrate as needed for withdrawal symptoms over the next 3 days; day 2 maximum dose is 12 mg of sublingual buprenorphine, day 3 maximum dose is 16 mg of sublingual buprenorphine.
• Taper: reduce the daily dose by 1 to 2 mg daily; the taper duration will last approximately 10 to 14 days.
• Selected adverse effects: sedation, headache, constipation, insomnia
Alpha$_2$-adrenergic agonist treatment
Clonidine
• Initial dose: 0.1 to 0.3 mg of oral clonidine
• Reassess and re-dose: reassess the patient every 2 to 4 hours; if the patient has withdrawal symptoms, give an additional 0.1 to 0.3 mg of oral clonidine; if the patient is hypotensive, somnolent, or with other signs of clonidine toxicity, do not give additional doses; typical doses are 0.1 to 0.3 mg every 6 to 8 hours.
• Taper: reduce the daily dose of clonidine by 0.1 to 0.2 mg per day; the taper duration will last approximately 10 to 14 days.
• Selected adverse effects: sedation, headache, hypotension, bradycardia
Adjunctive medications
• Diarrhea: anti-motility agents such as loperamide
• Nausea/vomiting: anti-emetics such as ondansetron
• Abdominal cramps: antispasmodics such as dicyclomine
• Muscle and joint aches: analgesics such as acetaminophen or ibuprofen
• Muscle spasms: antispasmodics such as cyclobenzaprine or baclofen
• Anxiety, irritability, and restlessness: anxiolytics such as lorazepam
• Insomnia: sleeping medication such as trazodone

[a]Buprenorphine-naloxone can be used instead of buprenorphine; buprenorphine can result in opioid withdrawal and should be used only in patients with clear evidence of opioid withdrawal.

NOTE: Abbreviation: EKG, electrocardiogram.

30% will be discharged against medical advice.[15,16] In hospitalizations when patients are administered methadone for management of withdrawal, there is a significant reduction in discharges against medical advice.[16] This may suggest that treatment of withdrawal has the added benefit of preventing discharges against medical advice, and the authors postulate that treatment may decrease surreptitious drug use during hospitalizations, although this has not been studied.

There are 2 approaches to treating opioid withdrawal—opioid substitution treatment and alpha$_2$-adrenergic agonist treatment (Table 1).[4,17-20] Of note, opioid substitution treatment, especially when using buprenorphine, should be started only when a patient has at least mild withdrawal symptoms.[20]

An important exception to the treatment approach listed in Table 1 occurs when a patient is already taking methadone or buprenorphine maintenance therapy. In this circumstance, the outpatient dose should be continued after confirmation of dose and timing of last administration with outpatient clinicians. It is important that clear communication with the patient's addiction clinician occurs at admission and discharge to prevent an inadvertently duplicated, or missed, dose.

Factors to consider when selecting a withdrawal treatment regimen include comorbidities, anticipated length of stay, anticipated discharge setting, medications, interest in long-term addiction treatment, and other patient-specific factors. In general, treatment with methadone or buprenorphine is preferred, because they are better tolerated and may be more effective than clonidine.[21-24] The selection of methadone or buprenorphine is often based on physician or patient preference, presence of contraindications, or formulary restrictions, as they have similar efficacy in the treatment of opioid withdrawal.[23] In cases where opioid replacement therapy is contraindicated, such as in an individual who has received naltrexone, clonidine should be used.[24]

Methadone and buprenorphine are controlled substances that can be prescribed only in outpatients by certified clinicians. Therefore, hospitalists are prohibited from prescribing these medications at discharge for the treatment of OUD. However, inpatient clinicians are exempt from these regulations and may provide both medications for maintenance and withdrawal treatment in the inpatient setting.

As such, while a 10 to 14-day taper may be optimal in preventing relapse and minimizing withdrawal, patients are often medically ready to leave the hospital before their taper is completed. In these cases, a rapid taper over 3 to 5 days can be considered. The disadvantage of a rapid taper is the potential for recrudescence of withdrawal symptoms after discharge. Individuals who do not tolerate a rapid taper should be treated with a slower taper, or transitioned to a clonidine taper.

Many hospitals have protocols to help guide the inpatient management of withdrawal, and in many cases, subspecialist consultation is not necessary. However, the authors recommend involvement of an addiction specialist for patients in whom management of withdrawal may be complicated. Further, we strongly encourage hospitalists to be involved in creation and maintenance of withdrawal treatment protocols.

Medication-Assisted Treatment

It is important to recognize that treatment of withdrawal is not adequate to prevent long-term opioid misuse.[25] The optimal long-term management of OUD includes the use of medication-assisted treatment (MAT). The initiation and titration of MAT should always be done in conjunction with an addiction specialist or buprenorphine-waivered physician who will ensure continuation of MAT as an outpatient. This means that, while hospitalists may be critical in facilitating linkage to MAT, in general, they will not have a significant role in the long-term management of OUD. However, hos-

pitalists should be knowledgeable about MAT because it is relatively common and can complicate hospitalizations.

There are two types of MAT: opioid-agonist treatment (OAT) and opioid-antagonist treatment. Opioid-agonist treatment involves the use of methadone, a long-acting opioid agonist, or buprenorphine, a long-acting partial opioid agonist. These medications decrease the amount and severity of cravings and limit the euphoric effects of subsequent opioid use.[17] Compared to abstinence-based treatment, OAT has been associated with increased retention in addiction treatment and employment, and reductions in incarceration, human immunodeficiency virus transmission, illicit drug use, opioid-overdose events, and mortality.[26-32] An alternative to OAT is naltrexone, an opioid antagonist. Naltrexone for OUD is administered as a monthly depot injection that prevents the user from experiencing opioid intoxication or dependence, and is associated with sustained abstinence.[17,33,34] The authors strongly recommend that hospitalists discuss the benefits of MAT with hospitalized individuals with OUD. In addition, when appropriate, patients should receive consultation with, or referral to, an addiction specialist.

Adverse Effects of Methadone, Buprenorphine, and Naltrexone

The benefits of MAT are substantial, but there are adverse effects, potential drug-to-drug interactions, and patient-specific characteristics that may impact the inpatient management of individuals on MAT. Selected adverse effects of OAT are listed in Table 1. The adverse effects of naltrexone include nausea, vomiting, and transaminitis. It should also be noted that the initiation of buprenorphine and naltrexone may induce opioid withdrawal when administered to an opioid-dependent patient with recent opioid use. To avoid precipitating withdrawal, buprenorphine should be used only in individuals who have at least mild withdrawal symptoms or have completed detoxification,[20] and naltrexone should be used only in patients who have abstained from opioids for at least 7 to 10 days.[35]

Opioid-agonist treatments are primarily metabolized by the cytochrome P450 3A4 isoenzyme system. Medications that inhibit cytochrome P450 3A4 metabolism such as fluconazole can result in OAT toxicity, while medications that induce cytochrome P450 3A4 metabolism such as dexamethasone can lead to withdrawal symptoms.[18] If these interactions are unavoidable, the dose of methadone or buprenorphine should be adjusted to prevent toxicity or withdrawal symptoms. The major drug interaction with naltrexone is ineffective analgesia from opioids.

Another major concern with MAT is the risk of overdose-related deaths. As an opioid agonist, large doses of methadone can result in respiratory depression, while buprenorphine alone, due to its partial agonist effect, is unlikely to result in respiratory depression. When methadone or buprenorphine are taken with other substances that cause respiratory depression, such as benzodiazepines or alcohol, the risk of respiratory depression and overdose is significantly increased.[36,37] Overdose-related death with naltrexone usually occurs after the medication has metabolized and results from a loss of opioid tolerance.[38]

Special Populations

Medication-assisted treatment in individuals with acute pain. Maintenance treatment with OAT does not provide sufficient analgesia to treat episodes of acute pain.[39] In patients on methadone maintenance, the maintenance dose should be continued and adjunctive analgesia should be provided with nonopioid analgesics or short-acting opioids.[39] The management of acute pain in individuals on buprenorphine maintenance is more complicated since buprenorphine is a partial opioid agonist with high affinity to the opioid receptor, which limits the impact of adjunctive opioids. The options for analgesia in buprenorphine maintenance treatment include 1) continuing daily dosing of buprenorphine and providing nonopioid or opioid analgesics, 2) dividing buprenorphine dosing into a 3 or 4 times a day medication, 3) discontinuing buprenorphine and treating with opioid analgesics, 4) discontinuing buprenorphine and starting methadone with nonopioid or opioid analgesics.[39] In cases where buprenorphine is discontinued, it should be restarted before discharge upon resolution of the acute pain episode. An individual with acute pain on naltrexone may require nonopioid analgesia or regional blocks. In these patients, adequate pain control may be challenging and require the consultation of an acute pain specialist.

Pregnant or breastfeeding individuals. Opioid misuse puts the individual and fetus at risk of complications, and abrupt discontinuation can cause preterm labor, fetal distress, or fetal demise.[40] The current standard is to initiate methadone in consultation with an addiction specialist.[40] There is evidence that buprenorphine can be used during pregnancy; however, buprenorphine-naloxone is discouraged.[18,40] Of note, use of OAT in pregnancy can result in neonatal abstinence syndrome, an expected complication that can be managed by a pediatrician.[40]

Methadone and buprenorphine can be found in low concentrations in breast milk.[41] However, according to the Academy of Breastfeeding Medicine's clinical guidelines, women on stable doses of methadone and buprenorphine should be encouraged to breastfeed.[41] Naltrexone enters breast milk and has potential adverse effects for the newborn. Either the mother should discontinue naltrexone or should not breastfeed.[35]

Treatment of polysubstance misuse. Individuals with OUD may also misuse other substances. The concomitant use of opioids and other central nervous system depressants, such as alcohol and benzodiazepines, is especially worrisome as they can potentiate respiratory depression. The presence of polysubstance misuse does not preclude the use of MAT for the treatment of OUD. In those with comorbid alcohol use disorder, the use of naltrexone may be appealing as it can treat both alcohol use disorder and OUD. Given the complexities of managing polysubstance misuse, addiction

specialists should be involved in the care of these patients.[42] In addition, patients should be educated on the risks of polysubstance misuse, especially when it involves 2 central nervous system depressants.

Comorbid medical disease. In general, medical comorbidities do not significantly affect the treatment of OUD; however, dysfunction of certain organ systems may necessitate a dose reduction or discontinuation of MAT. Severe liver disease may result in decreased hepatic metabolism of OAT.[35,42] Prolonged QTc, or history of arrhythmia, may preclude the use of methadone.[17,35,42] In addition, chronic hypercapnic respiratory failure or severe asthma may be contraindications for the use of methadone in an unmonitored setting.[35] Kidney failure is not known to be a contraindication to MAT, and there is no consensus on the need for dose reduction of MAT with decreasing glomerular filtration rate; however, some authors recommend a 25% to 50% dose reduction of methadone when the glomerular filtration rate is less than 10 milliliters per minute.[43] There is no such recommendation with buprenorphine, although it has not been adequately studied in individuals with renal failure. Close monitoring for evidence of toxicity is prudent in individuals on MAT with acute or chronic renal failure.[35]

Rural or resource-limited areas. There is a significant shortage of addiction treatment options in many regions of the United States. As of 2012, there were an estimated 2.3 million individuals with OUD; however, more than 1 million of these individuals do not have access to treatment.[44] As a result, many addiction treatment programs have wait lists that can last months or even years.[45] These shortages are especially apparent in rural areas, where individuals with OUD are particularly reliant upon buprenorphine treatment because of prohibitive travel times to urban-based programs.[46] To address this problem, new models of care delivery are being developed, including models incorporating telemedicine to support rural primary care management of OUD.[47]

The Future of Medication-Assisted Treatment

Currently, MAT is initiated and managed by outpatient addiction specialists. However, evidence supports initiation of MAT as an inpatient.[48] A recent study compared inpatient buprenorphine detoxification to inpatient buprenorphine induction, dose stabilization, and postdischarge linkage-of-care to outpatient opioid treatment clinics. Patients who received inpatient buprenorphine initiation and linkage-of-care had improved buprenorphine treatment retention and reported less illicit opioid use.[48] The development of partnerships between hospitals, inpatient clinicians, and outpatient addiction specialists is essential and could lead to significant advances in treating hospitalized patients with OUD.

The initiation of MAT in hospitalized patients with immediate linkage-of-care shows great promise; however, at this point, the initiation of MAT should be done only in conjunction with addiction specialists in patients with confirmed outpatient follow-up. In cases where inpatient MAT initiation is pursued, education of staff including nurses and pharmacists is essential.

TABLE 2. Harm Reduction Strategies[50]

Safer injection education

1. Find a safe environment and a partner to monitor for signs of opioid overdose.
2. Wash hands and sterilize work surfaces.
3. Place heroin into sterile cooker or spoon.
4. Use sterile water to dissolve heroin.
   - If sterile water is not available, boil water for 10 minutes before using. If this is not an option, then use bottled water or water from a clean tap. Do not use standing water, such as from a toilet bowl or puddle.
5. Heat cooker or spoon to dissolve heroin.
   - Sometimes acidification is necessary to fully dissolve the heroin; if so, use citric acid or ascorbic acid powder. Do not use lemon juice as this can lead to a fungal infection.
6. Place a dense cotton pellet into the dissolved heroin to serve as a filter.
   - Do not use cigarette filters as they contain glass particulates. Do not reuse or share cotton pellets.
7. Insert sterile needle into dense cotton pellet and draw back.
   - Use a sterile needle and syringe with every injection. Do not use another person's needles or share needles.
8. Clean the injection site with alcohol swab.
   - Do not lick the needle or skin prior to injecting.
9. Inject heroin.
10. Safely dispose of used supplies including needles and syringes.

Opioid overdose education

1. Recognize the signs of opioid overdose.
   - Deep sleeping that does not respond to shaking or attempts to wake up
   - Snoring, gurgling, or choking
   - No breathing or slow breathing (less than 1 breath per 5 seconds)
   - Blue or gray lips or fingernails
   - Pale, clammy skin
2. Contact emergency medical services. Tell emergency medical services that the person has overdosed on opioids. Alert emergency medical services if the person is not breathing
3. Administer naloxone.[a] Naloxone can be prescribed in different preparations (intramuscular and intranasal).
   - Intramuscular naloxone, 0.4 mg (1 mL)
     - Remove cap from naloxone vial, insert needle through rubber plug, pull 1 mL of naloxone into syringe, inject into a large muscle (upper arm, upper thigh, or buttocks), and safely dispose of syringe.
   - Intramuscular auto-injector naloxone (Evzio®), 0.4 mg
     - Visual and voice instructions help prompt through injection process; remove auto-injector from outer case, pull red safety guard, place the black end against the middle of the outer thigh (all right to go through clothing), and hold firmly in place for 5 seconds. There will be a click and a hiss sound meaning that naloxone has been administered. The needle will automatically retract into the case after use.
   - Intranasal naloxone, 2 mg
     - Pull off both end caps of syringe barrel, screw atomizer onto tip of syringe barrel, pull off end cap of naloxone cartridge and screw naloxone cartridge into syringe barrel, and insert into nose; push naloxone cartridge and empty half of cartridge into one nostril, then empty the rest of cartridge into the other nostril.
   - Intranasal naloxone (Narcan®), 4 mg
     - Remove nasal spray from package, place tip into nostril, and press plunger to release full dose into nostril.
4. Perform cardiopulmonary resuscitation and/or rescue breathing if needed.
5. Stay with the person until emergency medical services arrive.

[a]After 3 to 5 minutes, if there is no response to naloxone, another dose of naloxone can be administered. Naloxone should be kept on the person at all times. It should be stored at room temperature to avoid extreme temperatures (heat or cold) and light.

NOTE: Other illicit drugs can be injected and processes may vary.

Harm Reduction Interventions

Ideally, management of OUD results in abstinence from opioid misuse; however, some individuals are not ready for treatment or, despite MAT, have relapses of opioid misuse.

TABLE 3. Discharge Checklist for Patients with Opioid Use Disorder

All patients
• Do not prescribe concurrent opioids and benzodiazepines. Educate patients on the risk of overdose with concurrent opioid and benzodiazepine or alcohol use.
• Perform opioid overdose education to individuals at risk of opioid overdose and potential first responders. Prescribe naloxone to individuals at risk of opioid overdose. In states where law allows, distribute naloxone to potential first responders.
• In individuals who inject drugs, discuss safer injection practices and refer to a syringe exchange programs (if syringe exchange programs are available).
Patient with addiction specialist
• If the patient is on OAT, communicate the last dose of OAT and date of administration to the addiction specialist. If a weekend discharge, ensure that the patient is able to receive all doses of methadone or buprenorphine (ie, the clinic is open over the weekend).
Patient without addiction specialist
• Discuss OUD treatment, including psychosocial and psychotherapeutic interventions and MAT.
• Refer to addiction specialist. If possible, have appointment arranged prior to discharge.

NOTE: Abbreviations: MAT, medication-assisted treatment; OAT, opioid-agonist treatment; OUD, opioid use disorder.

Given this, a secondary goal in the management of OUD is the reduction of harm that can result from opioid misuse.

Many individuals inject opioids, which is associated with increased rates of viral and bacterial infections secondary to nonsterile injection practices.[49] Educating patients on sterile injection methods (Table 2),[50] including the importance of sterile-injecting equipment and water, and cleaning the skin prior to injection, may mitigate the risk of infections and should be provided for all hospitalized people who inject drugs.

Syringe-exchange programs provide sterile-injecting equipment in exchange for used needles, with a goal of increasing access to sterile supplies and removing contaminated syringes from circulation.[51] While controversial, these programs may reduce the incidence of human immunodeficiency virus, hepatitis C virus, and hepatitis B virus.[51]

In addition, syringe-exchange programs often provide addiction treatment referrals, counseling, testing, and prevention education for human immunodeficiency virus, hepatitis C virus, and sexually transmitted infections.[49] In the United States, there are 226 programs in 33 states (see https://nasen.org/directory for a list of programs and locations. Inpatient clinicians should provide a list of local resources including syringe-exchange programs at the time of discharge for any people who inject drugs. In addition, individuals with OUD are at increased risk for overdose, especially in the postdischarge setting due to decreased opioid tolerance.[52] In 2014, there were 28,647 opioid overdose-related deaths in the United States.[2] To address this troubling epidemic, opioid overdose education and naloxone distribution has been championed to educate patients at risk of opioid overdose and potential first responders on how to counteract an overdose by using naloxone, an opioid antagonist (see Table 2 for more information on opioid overdose education). The use of opioid overdose education and naloxone distribution has been observed to reduce opioid overdose-related death rates.[53]

Hospitalists should provide opioid overdose education and naloxone to all individuals at risk of opioid overdose (including those with OUD), as well as potential first responders where the law allows (more information including individual state laws can be found at http://prescribetoprevent.org).[20]

Considerations at Discharge

There are a number of considerations for the hospitalist at discharge (see Table 3 for a recommended discharge checklist). In addition, it is important to appreciate, and minimize, the ways that hospitalists contribute to the opioid epidemic. For instance, prescribing opioids at discharge in opioid-naïve patients increases the risk of chronic opioid use.[54] It is also essential to recognize that increased doses of opioids are associated with increased rates of opioid overdose-related deaths.[55] As such, hospitalists should maximize the use of nonopioid analgesics, prescribe opioids only when necessary, use the smallest effective dose of opioids, limit the number of opioid pills distributed to patients, and check prescription-monitoring programs for evidence of misuse.

CONCLUSION

Hospitalization serves as an important opportunity to address addiction in individuals with OUD. In addressing addiction, hospitalists should identify and intervene on psychosocial and mental health barriers, treat opioid withdrawal, and propagate harm reduction strategies. In addition, there is a growing role for hospitalists to be involved in the initiation of MAT and linkage-of-care to outpatient addiction treatment. If hospitalists become leaders in the inpatient management of OUD, they will significantly improve the care provided to this vulnerable patient population.

Disclosure: The authors report no financial conflicts of interest.

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Acute Pain Management in Hospitalized Adult Patients with Opioid Dependence: A Narrative Review and Guide for Clinicians

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Pain management is a core competency of hospital medicine, and effective acute pain management should be a goal for all hospital medicine providers. The prevalence of opioid use in the United States, both therapeutic and non-medical in origin, has dramatically increased over the past decade. Although nonopioid medications and nondrug treatments are essential components of managing all acute pain, opioids continue to be the mainstay of treatment for severe acute pain in both opioid-naïve and opioid-dependent patients. In this review, we provide an evidence-based approach to appropriate and safe use of opioid analgesics in treating acute pain in hospitalized patients who are opioid-dependent. *Journal of Hospital Medicine* 2017;12:375-379. © 2017 Society of Hospital Medicine

Up to 40% of Americans experience chronic pain of some kind.[1] In the United States, opioid analgesics are the most prescribed class of medications,[2] with 245 million prescriptions filled in 2014 alone. Thirty-five percent of these prescriptions were for long-term therapy.[3] It is now apparent that opioid pain medication use presents serious risks. In 2014, 10.3 million persons reported using prescription opioids for nonmedical reasons.[4] Between 1999 and 2014, more than 165,000 people in the United States died of overdose related to opioid medication.[5] In addition, heroin use in the United States has increased over the past decade.[6] Opioid agonist maintenance therapy is also increasingly used to treat patients with opioid use disorder.

Given the prevalence of opioid use in the United States, it is important for hospitalists to be able to appropriately and safely manage acute pain in patients who have been exposed long-term to opioids, whether it is therapeutic or non-medical in origin. Although nonopioid medications and nondrug treatments are essential components of managing all acute pain, opioids continue to be the mainstay of treatment for severe acute pain in both opioid-naïve and opioid-dependent patients.

Given the paucity of published trials meeting the typical criteria, we did not perform a structured meta-analysis but, instead, a case-based narrative review of the relevant published literature. Our goal in performing this review is to guide hospitalists in the appropriate and safe use of opioid analgesics in treating acute pain in hospitalized patients who are opioid-dependent.

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Received: October 26, 2016; **Revised:** December 19, 2016; **Accepted:** January 1. 2017

2017 Society of Hospital Medicine DOI 10.12788/jhm.2733

DEFINITIONS

When managing acute pain in patients with opioid dependence it is important to have a clear understanding of the definitions related to opioid use. Addiction, physical dependence and tolerance have been defined by a joint consensus statement of the American Society of Addiction Medicine, American Academy of Pain Medicine, and American Pain Society[7]: *Addiction* is a primary, chronic, biological disease, with genetic, psychosocial and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving.

Physical Dependence is a state of adaptation that is manifested by a drug class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.

Tolerance is the state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time.

Opioid use disorder (OUD) is defined as a problematic pattern of opioid use leading to clinically significant impairment or distress with symptoms including a strong desire for opioids, inability to control or reduce use of opioids, continued use despite adverse consequences, and development of tolerance and withdrawal symptoms.[8]

PATHOPHYSIOLOGY

Physical dependence and tolerance are common consequences of long-term opioid use. In contrast, OUD has been reported to affect only 2% to 6% of individuals exposed to opioids.[9] The underlying mechanisms that lead an individu-

TABLE 1. Equianalgesic Doses of Opioid Medications

Medication	Oral Dose, mg	Parenteral Dose, mg
Morphine	30	10
Hydrocodone	30	NA
Hydromorphone	7.5	1.5
Diacetylmorphine (heroin)	NA	4
Fentanyl	NA	0.1
Buprenorphine	2	0.4
Methadone	Morphine equivalents to methadone <100 mg - 3:1 101-300 mg - 5:1 301-600 mg - 10:1 601-800 mg - 12:1 801-1000 mg - 15:1 >1000 mg - 20:1	10

NOTE: Abbreviation: NA, not available.

al to abuse or become addicted to opioids largely due to the effects opioids have on endogenous μ-opioid receptors. As analgesics, opioids exert their effects by binding primarily to these μ-opioid receptors, with a large concentration in the brain regions regulating pain perception.[10,11] There is also a large concentration of μ-opioid receptors in the brain reward regions, leading to perceptions of pleasure and euphoria. Repeated administration of opioids conditions the brain to a learned association between receiving the opiate and euphoria.[12,13] This association becomes stronger as the frequency and duration of administration increases over time, ultimately leading to the desire or craving of the opioid's effect.

The effect of tolerance also contributes to the pathophysiology of opioid abuse as it leads to a decrease in opioid potency with repeated administration.[14-16] To achieve analgesia as well as the reward effect, opioid dosage and/or frequency must be increased, strengthening the association between receipt of opioid and reward. Tolerance to the reward effect occurs quickly, whereas tolerance to respiratory depression occurs much more slowly.[17] This mismatch in tolerance of effect may lead to increase in opioid doses to maintain analgesia or euphoria, and also places patients at a higher risk of overdose.[18]

ACUTE PAIN MANAGEMENT

Clinical Example: Heroin User

A 47-year-old man is admitted with fever, chills, and severe mid-back pain and receives a diagnosis of sepsis. The patient admits to using intravenous heroin 500 mg (five 100 mg "bags") on a daily basis. He is admitted, fluid resuscitated and started on broad spectrum antibiotics. Blood cultures quickly grow *Staphylococcus aureus*. Magnetic resonance imaging of the spine shows cervical vertebral osteomyelitis. On examination, the patient is diaphoretic and complains of diffuse myalgias and diarrhea. The patient's back pain is so severe that he cannot ambulate. What is the best way to manage this patient's acute pain and communicate with him about his pain management?

Managing acute pain in a patient using heroin can be challenging for many reasons. First, both physicians and pharmacists report a lack of confidence in their ability to prescribe opioids safely or to treat patients with a history of opioid abuse.[19] Second, there is a paucity of evidence in treating acute pain in heroin users. Finally, due to the clandestine manufacturing of illicit drugs, the actual purity of the drug is often unknown making it difficult to assess the dose of opioids in heroin users. Drug Enforcement Agency seizure data indicate a wide range of heroin purity: 30% to 70%.[20]

In the hospital setting, acute pain is often undertreated in patients with a history of active opioid abuse. This may be due to providers' misconceptions regarding pain and behavior in opioid addicts, including worrying that the patient's pain is exaggerated in order to obtain drugs, thinking that a regular opioid habit eliminates pain, believing that opioid therapy is not effective in drug addicts, or worrying that prescribing opioids will exacerbate drug addiction.[21] Data demonstrates that the presence of opioid addiction seems to worsen the experience of acute pain.[22] These patients also often have a higher tolerance and thus require higher dosages and more frequent dosing of opioids to adequately treat their pain.[23]

Converting daily heroin use to morphine equivalents is necessary to establish a baseline analgesic requirement and to prevent withdrawal. It is challenging to convert illicit heroin to morphine equivalents however, as one must take into account the wide variation in purity and understand that the stated use of heroin (e.g. 500 mg daily) reflects weight and not dosage of heroin.[20]

In these patients, treatment of acute pain should be individualized according to presenting illness and comorbidities. Previous data and an average purity of 40% suggest that the parenteral morphine equivalent to a bag of heroin (100 mg) is 15 to 30 mg.[20,24,25] Common equianalgesic doses of opioid medications are listed in Table 1. Because of increased tolerance, the frequency of administration should be shortened, from every 4 hours to every 2 or 3 hours. Except for a shorter onset of action, there has not been a difference shown in superiority between oral and parenteral routes of administration. Finally, patients should receive both long-acting basal and short-acting as-needed analgesics based on their daily use of opioids.[23]

In our clinical example, IV heroin 500 mg daily converts to parenteral morphine 75 to 150 mg every 24 hours. We recommend initiating IV morphine 10 mg every 3 hours as needed for pain and withdrawal symptoms, with early reassessment regarding need for a higher dose or a shorter frequency based on symptoms. Nonopioid analgesics should also be administered with the goal of decreasing the opioid requirement. As soon as possible, the patient should be changed to oral basal and short-acting opioids as needed for breakthrough pain. The appropriate dose of long acting basal analgesia can be determined the following day based on the patient's total daily dose (TDD) of opioids. An example of converting from

TABLE 2. Conversion of Parenteral Opioid Medications to Basal and Short-Acting Oral Regimen

Step	Patient Example
1. Add all opioid doses (1 time only, PRN, scheduled) within past 24 hours and convert to oral MEQs. To convert parenteral morphine dose to oral MEQs, multiply by a factor of three. Calculate TDD.	1. Within past 24 hours, patient received these orders: • IV morphine 6 mg × 6 doses • Acetaminophen/hydrocodone 325/7.5 mg × 2 doses • IV morphine 4 mg × 1 dose • IV morphine 40 mg = 120 mg oral MEQs • Hydrocodone 15 mg = 15 mg oral MEQ • TDD = 135 mg oral MEQ
2. Divide TDD into oral MSSR or similar long-acting opioid equivalent every 8-12 hours.	2. Start oral MSSR regimen: 45 mg Q8, or 60 mg Q12
3. Divide TDD into short-acting, oral, PRN medication: TDD/8 for Q3 dosing, or TDD/6 for Q4	3. Calculate short-acting PRN regimen: 135 mg/8 = 15 mg MSIR) Q3 PRN pain
4. Assess analgesia using institutional specific protocol and adjust both basal and short-acting medications. If there is no pain relief, increase TDD by 25% to 50%; if patient is too sedated, decrease TDD by 25% to 50%.	4. Next day, patient still complains of pain (9/10) and inadequate analgesia, despite taking all scheduled and PRN medications. • Increase TDD by 25% to 50%: 168-202 mg • Change Basal to 60 mg MSSR Q8 • Change short acting to 30 mg MSIR Q4 PRN pain

NOTE: Abbreviations: IV, intravenous; MEQ, morphine equivalents; MSIR; morphine sulfate immediate-release; MSSR, morphine sulfate sustained-release; PRN, as needed; TDD, total daily dose.

intravenous PRN morphine to oral basal and short acting opioids is shown in Table 2.

In communicating with a patient with opioid-use disorder with acute pain, it is best to outline the pain management plan at admission including: the plan to effectively treat the patient's acute pain, prevent opioid withdrawal symptoms, change to oral opioid analgesics as soon as possible, discussion of non-opioid and non-drug treatments, reinforcement that opioids will be tapered as the acute pain episode resolves, and a detailed plan for discharge Later in this article, we describe discharge planning.

Clinical Example: Patient on Chronic Opioid Therapy for Chronic Pain

A 64 year-old man was involved in a motorcycle accident and suffered a right distal tibia-fibula fracture and several broken ribs with a secondary pneumothorax. The patient's past medical history is significant for chronic low back pain for which he states he takes morphine sustained release 30 mg orally every 8 hours and morphine immediate release 15 mg orally four times daily for breakthrough pain. The patient states his pain is much worse than prior to the accident. Trauma surgery requests recommendations on appropriate pain management. What is the best way to manage this patient's acute pain and communicate with him about his pain management?

When treating acute pain in patients with chronic pain on opioid therapy, it is vital to establish the patient's baseline pain level and to accurately reconcile the patient's outpatient daily opioid use. The patient's prescription record should be verified in the state's prescription drug monitoring program. On admission, a urine drug test should be obtained to assess for use of other potential illicit substances (eg, cocaine). Patients who test positive for illicit substances are at high risk for a substance use disorder. Management and discharge plans should be as outlined in the above case. It is important to know that the first-tier immunoassay urine toxicology screens used by hospitals test for natural opioids (morphine, codeine, heroin). Semi-synthetic (example, oxycodone) or synthetic (example, fentanyl) opioids are unlikely to be detected and thus the urine drug screen may not be helpful to determine adherence to certain prescription opioids. Gas chromatography/mass spectrometry is the most sensitive and specific type of urine screen and can be ordered to confirm a prescribed opioid if needed.[26]

Pain management should begin with calculating the TDD of oral opioids that the patient was taking prior to admission, and converting to morphine equivalents. For moderate acute pain, TDD can be increased by 25% to 50%. The revised TDD can then be prescribed as a long-acting opioid every 8 to 12 hours to provide basal analgesia. The dose of additional immediate-release medication available throughout the day to manage breakthrough pain is determined by dividing the new TDD into every 3 to 4 hours as-needed dosing (Table 2).

If severe pain is anticipated, patient controlled analgesia (PCA) is an effective alternative to deliver opioids. The use of PCA allows self-titration, on demand analgesia, and minimizes the likelihood of under-dosing the patient.[27] The revised TDD is a useful starting point when calculating the PCA dosage regimen. Ideally, the revised TDD should be prescribed as a long acting oral opioid medication every 8 to 12 hours for basal analgesia, with PCA administered as an as-needed bolus. If a patient cannot tolerate oral medications, PCA can provide continuous infusion of medication to provide basal analgesia, though the risk of oversedation and respiratory depression is increased.[28]

For our clinical example, we recommend increasing the preadmission TDD of opioids (180 mg morphine equivalents) by 25% (225 mg) and administering as morphine 75 mg sustained-release every 8 hours to provide baseline analgesia and prevent withdrawal symptoms. The acute pain can be managed by initiating morphine PCA without continu-

TABLE 3. Methadone and Buprenorphine Pharmacology

	Methadone	Buprenorphine
Mechanism of action	Mu receptor agonist, weak NMDA receptor antagonist	Mu receptor partial agonist, kappa receptor antagonist
Duration of analgesia	Short term (<5-7 d): 4-8 h Long term (>1-2 wk): 22-48 h	Parenteral: 4-8 h Sublingual: 24-36 h
Half-life	35-48 h (range, 9-87 h)	Parenteral: 2-3 h Sublingual: 27-37 h
Starting dose	10-30 mg divided Q8-12 h	Sublingual: 4-8 mg daily
Maintenance dose	50-80 mg daily	16-24 mg daily

NOTE: Abbreviation: NMDA, N-methyl-D-aspartate.

ous infusion at 0.5 mg bolus every 8 minutes as needed for breakthrough pain or oral morphine 30 mg immediate-release tablets every 3 hours as needed for pain. The patient should be assessed frequently, and naloxone kept readily available. In addition, nonopioid and nondrug treatments should be optimized.

When communicating with patients with underlying chronic pain on chronic opioid therapy, it is important to discuss the treatment plan early, including addressing that they will likely not be pain free during their hospitalization, but rather goals of pain relief and improved function should be established. The plan to change to oral opioid analgesics as soon as possible and importance of multi-modal treatment should be emphasized. The patient should be informed that medication changes are for the short-term only and that the underlying chronic pain will likely remain unchanged.

Clinical Example: Patient on Medication-Assisted Therapy

A 42-year-old woman presents with acute epigastric pain and receives a diagnosis of acute gallstone pancreatitis. She states that her pain is very severe and appears uncomfortable. Her past medical history is significant for heroin addiction, but she has been successfully treated for opioid-use disorder with buprenorphine 16 mg daily for the past three years. What is the best way to manage this patient's acute pain and communicate with her about her pain management?

Medication-assisted therapies (MATs) for treatment of opioid abuse, which include methadone and buprenorphine (Table 3), have been shown to be effective in helping patients recover in opioid-use disorder, are cost-effective and reduce the risk of opioid overdose.[29] However, treatment for acute pain in patients who are receiving methadone or buprenorphine MAT is a challenge because of pharmacokinetic changes that occur with prolonged use. It is important to know that patients receiving opioid agonist MAT are usually treated with 1 dose every 24 to 48 hours and do not receive sustained analgesia.[30]

In the case of patients on methadone as MAT, the methadone should be continued at the prescribed daily dose and additional short-acting opioid analgesics given to provide appropriate pain relief.[27,31] Because of opioid tolerance, patients receiving MAT often require increased and more frequent doses of short-acting opioid analgesics to achieve adequate pain control.

Buprenorphine is a mu-opioid receptor partial agonist. The partial agonist properties of buprenorphine result in a "ceiling effect" that limits maximal analgesic and euphoric potential. Buprenorphine's high affinity for the mu receptor also may result in competition with full opioid agonist analgesics, creating a challenge in treating acute pain. Because of the erratic dissociation of buprenorphine from the mu receptor, naloxone should be available and patients should be frequently monitored when the two agents are administered together. Recommendations regarding acute pain management in patients being treated with buprenorphine are largely based on expert opinion. Treatment options include[32-34]:

- Continue maintenance therapy with buprenorphine and treat acute pain with short acting opioid agonists. Higher doses of opioid agonists and more frequent dosing may be needed to provide adequate pain relief since they compete with buprenorphine at the mu receptor. Opioids with higher affinity for the mu receptor (morphine, hydromorphone, fentanyl) may be more efficacious.
- Discontinue buprenorphine and treat the patient with scheduled full opioid analgesics, titrating the dose initially to try to avoid withdrawal and then to provide pain relief. The partial agonism of the mu-receptor from buprenorphine and the blockade of other opioids can persist for as long as 72 hours. During this period, close monitoring and keeping naloxone available are important. When acute pain resolves, discontinue full opioid agonist therapy and resume buprenorphine using an induction protocol.

For our clinical example, we recommend continuing buprenorphine at 16 mg daily, optimizing nonopioid treatment strategies, and using a higher dose parenteral full opioid agonist every 3 hours as needed to achieve adequate analgesia. The patient should be frequently monitored for adverse effects, and naloxone kept available. Full opioid analgesics should be tapered and discontinued as the acute pain resolves. The patient should be reassured that there is no evidence that using opioids to treat acute pain episodes increases the risk of relapse and that untreated acute pain is a more likely trigger for relapse. The patient's buprenorphine provider should be contacted at admission to verify dose as well as at discharge.

DISCHARGE PLANNING AND MANAGEMENT

Early discharge planning is essential for appropriate and safe management of acute pain in hospitalized patients

with opioid dependence. The major goals are to treat acute pain effectively, improve function, and return care to the patient's usual treating physician or methadone clinic. Patients on chronic opioid therapy often have a written opioid treatment agreement specifying only 1 prescriber. Therefore, verbal communication with the patient's authorized prescriber at admission and at discharge is essential, particularly given that the discharge summary may not be available at follow-up. Additional or higher doses of opioids should not be prescribed at discharge unless discussed with the patient's authorized prescriber. If it is believed necessary to provide opioid medication at discharge it should only be provided for a short period: 3 to 7 days.[35] Patients with OUD should be referred for addiction treatment, including MAT, and should be educated on harm-reduction strategies, including safe injecting, obtaining clean needles, and recognizing, avoiding, and treating opioid overdose. Prescribing intranasal naloxone should be strongly considered for patients with OUD and for patients who are taking more than 50 mg oral morphine equivalents for chronic pain.[34]

CONCLUSION

Management of acute pain in opioid-dependent patients is a complex and increasingly common problem encountered by hospitalists. In addition, given the OUD epidemic in the United States, safe opioid prescribing has become a paramount goal for all physicians. Although acute pain management will be individualized and will encompass clinical judgment, this review provides an evidence-based guide to effective and safe acute pain management and optimal opioid prescribing for hospitalized opioid-dependent patients.

Disclosure: Nothing to report.

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Diagnostic Testing in AKI: Let's Move the Field Forward

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In this issue of the *Journal of Hospital Medicine*, Lusica et al.[1] discuss the utility of urine eosinophils (UEs) in evaluating for acute interstitial nephritis (AIN) in patients with acute kidney injury (AKI), an important and oft-confused concern in medicine. I can't think of a more appropriate topic for the "Things We Do for No Reason" (TWDFNR) series. Numerous tests are ordered in the evaluation of AKI.[2] Many, such as batteries of serological tests, are unnecessary and add little diagnostic information. Some, such as UEs and fractional excretion of sodium (FENa), provide misinformation. And others, such as contrast-enhanced computed tomography scans, are potentially harmful.[2] In a previous TWDFNR article, the limitations of FENa in the evaluation of AKI were reviewed.[3] There are common threads linking the shortcomings of UEs and FENa and even new diagnostic tests. What are the lessons from these studies, and how might clinicians best apply them in their practice?

As reviewed in this issue, UE testing is employed in AKI to evaluate for hospital-acquired AIN. Small initial studies led to widespread use of this test, despite methodological flaws.[4] A later, definitive study involving 566 patients who had both UEs and kidney biopsies performed within the same week demonstrated that UEs offered no diagnostic value in AKI.[5] The same pattern occurred in the increased use of FENa to distinguish prerenal azotemia from acute tubular necrosis in AKI patients.[3] Small studies in highly select patients supported its use for this purpose.[6] Subsequently, larger studies in more diverse populations noted that FENa was associated with many false positive and negative results,[6] likely due to more widespread use of this test in disease states such as cirrhosis, congestive heart failure, chronic kidney disease, and diabetes, which were not included in initial studies.

It is apparent that clinicians have been led astray by small, flawed positive studies employed in highly selected populations. These initial positive studies based on excessively large effect size estimates were subsequently shown to be negative in larger studies with more plausible effect sizes. Examples of this error are seen in publications involving prophylactic measures to reduce contrast nephrotoxicity.[7] Early studies on N-acetylcysteine administration prior to radiocontrast exposure showed positive results. Examination of these studies, however, demonstrates 2 key problems: 1) inclusion of small numbers of patients due to power calculations based on excessively large effect sizes, and 2) use of clinically unimportant endpoints such as serum creatinine changes.[7] The same issue complicates studies evaluating isotonic sodium bicarbonate vs. normal saline for contrast prophylaxis.[7]

The past 10-plus years have seen a proliferation of studies evaluating the utility of novel biomarkers for early diagnosis and prognosis in AKI. Have we fallen down the same rabbit hole in evaluating these new diagnostic tests for AKI? There is reason for concern if we examine published studies of novel biomarkers in other areas of medicine. To this point, many highly cited novel biomarker studies used for various diagnostic purposes (eg, cancer, infection, cardiovascular disease) employed excessively large effect size estimates for postulated associations that resulted in small, underpowered studies with initially positive results.[8] Subsequent large studies and meta-analyses reported negative or modestly positive test results when examining these same associations.[8] But we may be moving in the right direction. An early urine biomarker publication from a small, single center study[9] revealed overly optimistic results (area under the curve [AUC], 0.998; sensitivity, 100%; specificity, 98%) for AKI prediction. Subsequent large, multicenter biomarker studies showed only modest improvement in their discriminative value when compared with traditional clinical models.[10] These results precluded U.S. Food and Drug Administration (FDA) approval of most novel biomarkers for clinical practice and they were not adopted. In 2014, the FDA approved the point-of-care urinary biomarker TIMP-2/IGFBP7 (NephroCheck®) for predicting risk of AKI based on fairly rigorous testing using larger numbers of patients, heterogeneous populations, and important clinical endpoints.[11] In a 522-patient discovery cohort, this biomarker had an AUC of 0.80 for AKI prediction, which was validated in a 722-patient cohort and subsequently followed by a 420-patient multicenter cohort study revealing similar test characteristics (AUC, 0.82; sensitivity, 92%; specificity, 46%).[11] A study involving 382 critically ill AKI patients noted that this biomarker had a hazard ratio of 2.16 (95% confidence interval [CI] 1.32 to 3.53) for predicting dialysis requirement or death.[11] And while this test has yet to find its clinical niche, its operating characteristics are well-studied and likely valid. While predicting AKI earlier does not currently result in effective therapy, it may allow more timely discontinuation or avoidance of potentially nephrotoxic medications, ultimately reducing the severity of AKI and its consequences.

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Received: December 9, 2016; **Accepted** December 10, 2016

2017 Society of Hospital Medicine DOI 10.12788/jhm.2735

In summary, clinicians should be aware of the strengths and limitations of diagnostic tests ordered in AKI patients, as seen with the overly optimistic results in small, flawed UE and FENa studies. While we have taken a step in the right direction with diagnostic and prognostic biomarkers for AKI, we must apply rigorous study design to diagnostic tests under evaluation before adopting them into clinical practice. Only then can we move the field forward and improve patient care.

Disclosure: Nothing to report.

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Moving Antibiotic Stewardship from Theory to Practice

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We both attend on the Infectious Disease consult team in Veterans Affairs (VA) Hospitals, and predictably the conversation on afternoon rounds often revolves around antibiotics. When we have those discussions, our focus is not on a need to "preserve antibiotics" so they might be available to some unknown patient in the future. Rather, we are working with the primary team to provide the very best treatment for the patient entrusted to our care in the bed right in front of us. We believe it is in this context—providing optimal patient care—that the current efforts in the United States to improve antibiotic use should be viewed.

The growing challenges posed by antibiotic-resistant infections and the related threat of *Clostridium difficile* infection combine to sicken more than 2 million people each year and contribute to the deaths of more than 25,000 patients.[1] Improving antibiotic use through antibiotic stewardship is often proposed to hospitalists as an important part of stemming this tide. While this is true, even as infectious disease specialists with strong interests in antimicrobial stewardship we do not find that pitch compelling when we are on clinical service.

What motivates us to optimize antibiotic use for our patients is the evidence that doing so will have direct and immediate benefits to the patients under our care. Improving antibiotic use has been proven to decrease a patient's risk of acquiring *C. difficile* infection or an antibiotic-resistant infection not at some ill-defined time in the future, but during their current hospital stay.[2,3] Even more important, support from antibiotic stewardship programs has been proven to improve infection cure rates and reduce the risk of treatment failure for hospitalized patients.[4] The bottom line of antibiotic stewardship is better patient care. Sometimes that means narrowing or stopping antibiotics to reduce the risks of adverse events. In other cases, like in the treatment of suspected sepsis, it means ensuring patients get broad spectrum antibiotics quickly.

The patient care benefits of improving antibiotic use led the Centers for Disease Control and Prevention (CDC) to issue a call in 2014 for all hospitals to have antibiotic stewardship programs, and to the development of The Core Elements of Hospital Antibiotic Stewardship Programs to support that effort. As of January 1, 2017, antibiotic stewardship programs that incorporate all the CDC core elements became an accreditation requirement of The Joint Commission, and the Centers for Medicare and Medicaid Services has proposed making the same requirement of all hospitals that participate in their payment programs.

This means the question is no longer whether we should have antibiotic stewardship efforts in hospitals, but how we can do this most effectively. As the physicians who provide the most care in hospitals, hospitalists are best positioned to turn stewardship theories into practice. The article from Graber et al.[5] in this issue of the *Journal of Hospital Medicine* provides some important information that can help busy hospitalists incorporate stewardship into daily practice. The authors reviewed their experience with implementing stewardship efforts in VA hospitals to see which specific interventions were most likely to translate into improved antibiotic use. Based on their findings, we offer some suggestions for three conditions: pneumonia, urinary tract infection (UTI), and skin and soft tissue infection (SSTI). Together, these conditions drive roughly two-thirds of all antibiotic use in US hospitals.[6]

STEWARDSHIP IN PRACTICE: PNEUMONIA

The literature on treatment of pneumonia is increasingly demonstrating that shorter use of antibiotics is often better.[7] Even though current guidelines recommend 5 to 7 days of antibiotics for uncomplicated community-acquired pneumonia, average durations of therapy are often longer.[8] Previous work published in the *Journal of Hospital Medicine* focused on improving antimicrobial documentation as well as access to local clinical guidelines and implementing a 72-hour antimicrobial "time out" by hospitalists.[9] When these multimodal interventions tailored for hospitalists were in place, utilization of antibiotics improved. Graber et al.[5] also found that facility educational programs for prudent antimicrobial use and frequency of de-escalation review were associated with decreased overall antimicrobial use. Providing vague recommendations on antibiotic course, or none at all, at discharge or sign-out can lead to unnecessary antibiotics or an extended course of them. Pneumonia-specific interventions could target duration by outlining antibiotic course in hospitalist progress notes and at hand-off.

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Received: February 17, 2017; **Accepted**: February 25, 2017

2017 Society of Hospital Medicine DOI 10.1002/jhm.2741

STEWARDSHIP IN PRACTICE: UTI

Misuse of antibiotics in UTI often stems from overtreatment of asymptomatic bacteriuria or unneeded diagnostic testing. Often, the pivotal step in avoiding unnecessary treatment lies in the ordering of the urine culture.[10] Graber et al.[5] showed that order sets were associated with decreased antimicrobial use. In the case of UTI, hospitalists could work with the stewardship team to design order sets that guide providers to appropriate reasons for ordering a urine culture. Order sets could also help providers recognize important patient-specific risks for certain antibiotics, such as the risk of *C. difficile* with fluoroquinolones in an elderly patient. Targeting different steps in overutilization of antibiotics would encompass more prescribers and could lead to reducing other unnecessary testing, which is a current focus for many hospitalists.

STEWARDSHIP IN PRACTICE: SSTI

Skin and soft tissue infections (SSTI) also offer a specific disease state to use order sets and education to improve duration of antibiotics, decrease overuse of broad spectrum antibiotics, and reduce unnecessary diagnostic studies. For example, gram negative and/or anaerobic coverage are rarely indicated in treating SSTIs but are often used. SSTI-specific order sets and guidelines have already been shown to improve both diagnostic work-up and antibiotic treatment.[11] As the providers who manage most of these infections in hospitals, hospitalists are ideally positioned to inform the development of SSTI order sets and pathways. The work by Graber et al.[5] provides some important insights into how we can effectively implement interventions to improve antibiotic use. These insights have never been more important as more hospitals move toward starting or expanding antibiotic stewardship programs. As leaders in patient safety and quality, and as the most important antibiotic prescribers in hospitals, hospitalists must play a central role in stewardship if we are to make meaningful progress.

Disclosure: Nothing to report.

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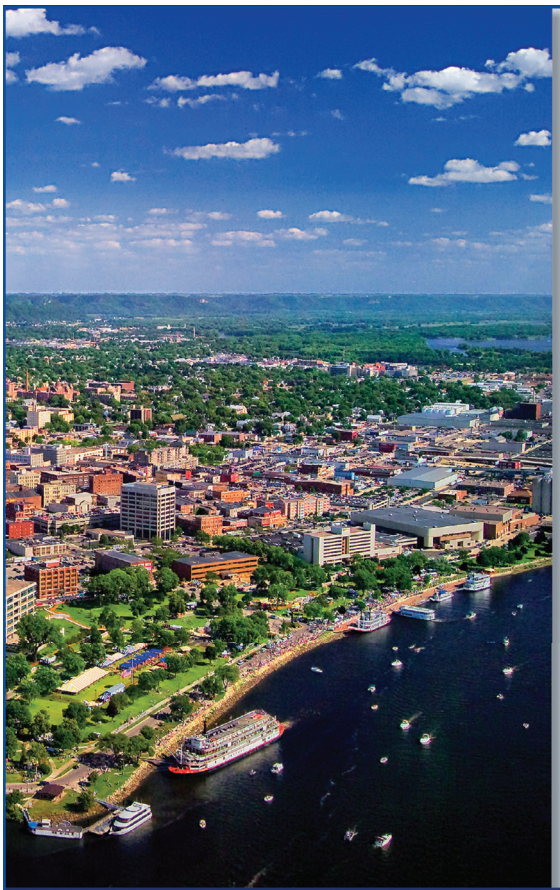

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- 7 on 7 off schedule (26 weeks per year) with majority of shifts less than 12 hours in length
- Collaborative, cohesive hospitalist team established in 2002 with high retention rate and growth
- 26-member internal medicine hospitalist team comprised of 16 physicians and 10 associate staff
- Primary responsibility is adult inpatient care
- Manageable daily census
- Excellent support and collegiality with subspecialty services
- Direct involvement with teaching family medicine and/or internal medicine residents
- Competitive compensation and benefits package, including loan forgiveness

La Crosse is a vibrant city, nestled along the Mississippi River. The historic downtown and riverfront host many festivals and events. Excellent schools and universities, parks, sports venues, museums and affordable housing make this a great place to call home.

For information contact Kalah Haug, Medical Staff Recruitment, at kjhaug@gundersenhealth.org. or (608) 775-1005.

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DIVISION HEAD OF HOSPITAL MEDICINE

The Henry Ford Medical Group (HFMG), one of the largest multispecialty group practices in the country, is seeking a highly qualified applicant to serve as Division Head in its Division of Hospital Medicine. With nearly 30 years of experience in Hospital Medicine, HFMG established a separate Division of Hospital Medicine in 2008, and is the largest Division in the Department of Medicine with over 50 hospitalist and palliative medicine faculty serving at three different hospitals.

Reporting to the Chair of Medicine, and in collaboration with hospital leaders and an experienced divisional leadership team, the Division Head will be responsible for the strategic direction, management, standardization, and coordination of the multi-site Division including:

- helping manage the continued expansion of the Divisional clinical enterprise
- recruitment, retention, and development of high quality clinical faculty
- continue the division's successful navigation of the value driven healthcare environment
- serve as a resource for Henry Ford Health System (HFHS) initiatives including observation medicine, physician advising, use of information technology, value based care, and improved patient experience

This is an excellent leadership opportunity with continued professional growth in a strong hospitalist group committed to the development of high quality hospitalists. The Division continues to be a leader in HFHS efforts to promote systemic integration/alignment, clinical excellence, innovation, and value in an accountable care environment.

The successful candidate will be ABIM certified (preference Internal Medicine with a Focused Practice in Hospital Medicine) and have at least 7 years of hospitalist practice experience with progressive proven leadership skills in a large hospitalist program preferably in an integrated healthcare organization. Strong clinical and communication skills are essential. Significant experience with quality and care management initiatives, operational management, as well as medical education are also desired.

Generous group practice benefits are provided including: vacation, CME time/allowance, insurance (life/disability/malpractice), and retirement package. A faculty appointment at Wayne State University School of Medicine is available commensurate with prior experience.

Review of applications will begin immediately and continue until the position is filled. Please submit your letter of interest and cv to Dr. Kimberly Baker-Genaw, Vice Chair of Medicine, in c/o Scott Johnson, Senior Physician Recruiter, at sjohns10@hfhs.org. For a detailed position description, please visit: http://p.rfer.us/HENRYFORDIHH1rb.

Henry Ford Health System is committed to the hiring, advancement and fair treatment of all individuals without regard to race, color, national origin, sex, sexual orientation, age, disability, religion, weight/height, marital status, familial status, veteran status or any other characteristic protected by law.

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Heather Gentile,
Phone: 973-290-8259
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Hospitalist/Nocturnist Opportunities

Cambridge Health Alliance (CHA) is a well respected, nationally recognized and award-winning public healthcare system, which receives recognition for clinical and academic innovations. Our system is comprised of three campuses and an integrated network of both primary and specialty care practices in Cambridge, Somerville and Boston's Metro North Region. CHA is a teaching affiliate of both Harvard Medical School (HMS) and Tufts University School of Medicine and opportunities for teaching medical students and residents are plentiful.

We are currently recruiting **BC/BE Hospitalist/Nocturnist** to join our division of approximately 20 physicians to cover inpatient services at both our Cambridge and Everett campuses. This position has both day and night clinical responsibilities. Ideal candidates with be FT (will consider PT), patient centered, posses excellent clinical/communication skills and demonstrate a strong commitment to work with a multicultural, underserved patient population. Experience and interest in performing procedures, as well as resident and medical student teaching is preferred. **All of our Hospitalists/Nocturnist hold academic appointments at Harvard Medical School**. At CHA we offer a supportive and collegial environment, a strong infrastructure, a fully integrated electronic medical record system (EPIC) and competitive salary/benefits package.

Please send CV's to Deanna Simolaris, Department of Physician Recruitment, Cambridge Health Alliance, 1493 Cambridge Street, Cambridge, MA 02139, via e-mail: dsimolaris@challiance.org, via fax (617) 665-3553 or call (617) 665-3555. www.challiance.org. We are an equal opportunity employer and all qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability status, protected veteran status, or any other characteristic protected by law.

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ABOUT US

Northwestern Medicine Lake Forest Hospital is a community hospital with nearly 200 beds and is located approximately 30 miles north of downtown Chicago in scenic and charming Lake Forest. Care is provided through the main hospital campus in Lake Forest and multiple outpatient facilities including one in Grayslake, IL, which also includes a free-standing emergency center. Lake Forest Hospital is served by a medical staff of more than 700 employed and affiliated physicians. It continues to be recognized by *U.S. News & World Report* as one of the top hospitals in Illinois and Chicago and also received Magnet re-designation in 2015, the gold standard for nursing excellence and quality care. A new state-of-the-art hospital facility is scheduled to open in 2017.

Northwestern Medicine Lake Forest Hospital

Northwestern Medicine is a growing, nationally recognized health system that provides world-class care at seven hospitals and more than 100 locations in communities throughout Chicago and the North and West suburbs. Together with Northwestern University Feinberg School of Medicine, we are pushing boundaries in our research labs, training the next generation of physicians and scientists, and pursuing excellence in patient care.

Our vision and values are deeply rooted in the idea that patients come first in all we do. We value building relationships with our patients and their families, listening to their unique needs while providing individualized primary, specialty and hospital-based care. Our recent affiliations and ongoing growth make it possible for us to serve more patients, closer to where they live and work.

Northwestern Memorial HealthCare, a nonprofit organization, is the corporate parent of Northwestern Medicine and all of its entities, including Northwestern Medicine Lake Forest Hospital, Northwestern Memorial Hospital, Northwestern Medicine Central DuPage Hospital, Northwestern Medicine Delnor Hospital, Northwestern Medicine Kishwaukee Hospital, Northwestern Medicine Valley West Hospital and Northwestern Medicine Marianjoy Rehabilitation Hospital.

If you are interested in advancing your career as an ICU Hospitalist with Northwestern Medicine Lake Forest Hospital, please e-mail your CV and cover letter to:

LFPCCRecruitment@nm.org

Hospitalists

Minnesota and Wisconsin

Be part of something bigger at HealthPartners, where we focus on health as it could be, affordability as it must be, and relationships built on trust. HealthPartners Medical Group (HPMG) is a large, nationally recognized multi-specialty physician practice, based at clinics and hospitals throughout metropolitan Minneapolis/St. Paul, central Minnesota and western Wisconsin.

Our Hospital Medicine Department is seeking BC/BE IM or FM physicians to work in our high functioning, multi-disciplinary team environment. Whether you seek an urban, suburban, semi-rural or rural community practice, HPMG has a variety of opportunities within thriving family-oriented communities with top school systems, healthy economies, sports and theatre and bountiful lakes and outdoor recreation.

- Regions Hospital is our tertiary hospital and regional referral center in St. Paul. We are a major teaching affiliate for the University of Minnesota with a dedicated Hospital Medicine Pathway in their residency program.
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