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An Academic Research Coach: An Innovative Approach to Increasing Scholarly Productivity in Medicine

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BACKGROUND: Academic faculty who devote most of their time to clinical work often struggle to engage in meaningful scholarly work. They may be disadvantaged by limited research training and limited time. Simply providing senior mentors and biostatistical support has limited effectiveness.

OBJECTIVE: We aimed to increase productivity in scholarly work of hospitalists and internal medicine physicians by integrating an Academic Research Coach into a robust faculty development program.

DESIGN: This was a pre-post quality improvement evaluation.

SETTING: This was conducted at the University of Washington in faculty across three academic-affiliated hospitals and 10 academic-affiliated clinics.

PARTICIPANTS: Participants were hospitalists and internists on faculty in the Division of General Internal Medicine at the University of Washington.

INTERVENTION: The coach was a 0.50 full time equivalent health services researcher with strong research methods, project implementation, and interpersonal skills. The coach consulted on research, quality improvement, and other scholarship.

MEASUREMENTS: We assessed the number of faculty supported, types of services provided, and numbers of grants, papers, and abstracts submitted and accepted.

RESULTS: The coach consulted with 49 general internal medicine faculty including 30 hospitalists who conducted 63 projects. The coach supported 13 publications, 11 abstracts, four grant submissions, and seven manuscript reviews. Forty-eight faculty in other departments benefited as co-authors.

CONCLUSION: Employing a dedicated health services researcher as part of a faculty development program is an effective way to engage clinically oriented faculty in meaningful scholarship. Key aspects of the program included an accessible and knowledgeable coach and an ongoing marketing strategy. *Journal of Hospital Medicine* 2019;14:457-461. Published online first April 8, 2019.

Historically, academic medicine faculty were predominantly physician-scientists.[1] During the past decade, the number of clinician-educators and nontenured clinicians has grown.[2] Many academically oriented clinical faculty at our institution would like to participate in and learn how to conduct quality scholarship. While institutional requirements vary, scholarly work is often required for promotion,[3] and faculty may also desire to support the scholarly work of residents. Moreover, a core program component of the Accreditation Council of Graduate Medical Education standards requires faculty to "maintain an environment of inquiry and scholarship with an active research component."[4] Yet clinical faculty often find academic projects to be challenging. Similar to residents, clinical academic faculty frequently lack formal training in health services research or quality improvement science, have insufficient mentorship, and typically have limited uncommitted time and resources.[5]

One approach to this problem has been to pair junior clinicians with traditional physician scientists as mentors.[6,7] This type of mentorship for clinical faculty is increasingly difficult to access because of growing pressure on physician-scientist faculty to conduct their own research, seek extramural funding, meet clinical expectations, and mentor fellows and faculty in their own disciplines.[8] Moreover, senior research faculty may not be prepared or have the time to teach junior faculty how to deal with common stumbling blocks (eg, institutional review board [IRB] applications, statistically testable hypothesis development, and statistical analysis).[8,9] Seminars or works-in-progress sessions are another strategy to bolster scholarly work, but the experience at our institution is that such sessions are often not relevant at the time of delivery and can be intimidating to clinical faculty who lack extensive knowledge about research methods and prior research experience.

Another approach to supporting the research efforts of academic clinicians is to fund a consulting statistician. However, without sufficient content expertise, statisticians may

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be frustrated in their efforts to assist clinicians who struggle to formulate a testable question or to work directly with data collected. Statisticians may be inexperienced in writing IRB applications or implementing protocols in a clinical or educational setting. Furthermore, statistical consultations are often limited in scope[10] and, in our setting, rarely produce a durable improvement in the research skills of the faculty member or the enduring partnership required to complete a longer-term project. Because of these shortcomings, we have found that purely statistical support resources are often underutilized and ineffective.

Other models to facilitate scholarship have been employed, but few focus on facilitating scholarship of clinical faculty. One strategy involved supporting hospitalist's academic productivity by reducing hospitalists' full-time equivalent (FTE) and providing mentorship.[11] For many, this approach is likely cost-prohibitive. Others have focused primarily on resident and fellow scholarships.[5,6]

In this report, we describe an educational innovation to educate and support the scholarly work of academic hospitalists and internists by using an academic research coach. We recruited a health researcher with extensive experience in research methods and strong interpersonal skills with the ability to explain and teach research concepts in an accessible manner. We sought an individual who would provide high-yield single consultations, join project teams to provide ongoing mentorship from conception to completion, and consequently, bolster scholarly productivity and learning among nonresearch clinicians in our Division. We anticipated that providing support for multiple aspects of a project would be more likely to help faculty overcome barriers to research and disseminate their project results as scholarly output.

METHODS

The coach initiative was implemented in the Division of General Internal Medicine at the University of Washington. The Division has over 200 members (60 hospitalists), including clinical instructors and acting instructors, who have not yet been appointed to the regular faculty (clinician-educators and physician scientists), and full-time clinical faculty. Division members staff clinical services at four area hospitals and 10 affiliated internal medicine and specialty clinics. Eligible clients were all Division members, although the focus of the initial program targeted hospitalists at our three primary teaching hospitals. Fellows, residents, students, and faculty from within and outside the Division were welcome to participate in a project involving coaching as long as a Division faculty member was engaged in the project.

Program Description

The overall goal of the coach initiative was to support the scholarly work of primarily clinical Division members. Given our focus was on clinical faculty with little training on research methodology, we did not expect the coach to secure grant funding for the position. Instead, we aimed to increase the quality and quantity of scholarship through publications, abstracts, and small grants. We defined scholarly work broadly: clinical research, quality improvement, medical education research, and other forms of scientific inquiry or synthesis. The coach was established as a 0.50 FTE position with a 12-month annually renewable appointment. The role was deemed that of a coach instead of a mentor because the coach was available to all Division members and involved task-oriented consultations with check-ins to facilitate projects, rather than a deeper more developmental relationship that typically exists with mentoring. The Division leadership identified support for scholarly activity as a high priority and mentorship as an unmet need based on faculty feedback. Clinical revenue supported the position.

Necessary qualifications, determined prior to hiring, included a PhD in health services or related field (eg, epidemiology) or a master's degree with five years of experience in project management, clinical research, and study design. The position also called for expertise in articulating research questions, selecting study designs, navigating the IRB approval process, collecting/managing data, analyzing statistics, and mentoring and teaching clinical faculty in their scholarly endeavors. A track record in generating academic output (manuscripts and abstracts at regional/national meetings) was required. We circulated a description of the position to Division faculty and to leadership in our School of Public Health.

Based on these criteria, an inaugural coach was hired (author C.M.M.). The coach had a PhD in epidemiology, 10 years of research experience, 16 publications, and had recently finished a National Institutes of Health (NIH) career development award. At the time of hiring, she was a Clinical Assistant Professor in the School of Dentistry, which provided additional FTE. She had no extramural funding but was applying for NIH-level grants and had received several small grants.

To ensure uptake of the coach's services, we realized that it was necessary to delineate the scope of services available, clarify availability of the coach, and define expectations regarding authorship. We used an iterative process that took into consideration the coach's expertise, services most needed by the Division's clinicians, and discussions with Division leadership and faculty at faculty meetings across hospitals and clinics. A range of services and authorship expectations were defined. Consensus was reached that the coach should be invited to coauthor projects where design, analysis, and/or substantial intellectual content was provided and for which authorship criteria were met.[12] Collegial reviews by the coach of already developed manuscripts and time-limited, low-intensity consultations that did not involve substantial intellectual contributions did not warrant authorship.[12] On this basis, we created and distributed a flyer to publicize these guidelines and invite Division members to contact the coach (Figure 1).

The coach attended Division, section, and clinical group meetings to publicize the initiative. The coach also individually met with faculty throughout the Division, explained her role, described services available, and answered questions. The marketing effort was continuous and calibrated with more or less exposure depending on existing projects and the coach's

Academic Research Coach
Services and Consultations

Who is the Coach?

{Name} is a PhD epidemiologist with 10 years' experience designing, conducting, and publishing clinical research. She is here to help you.

Why use the Coach?

The Academic Research Coach (ARC) is here to facilitate success in your scholarly activities. The ARC can help elevate methodological, statistical and research implementation aspects of your projects.

Consultations

Who can use the ARC? Faculty in the Division of General Internal Medicine at UWMC, Harborview, and the VA.

Consultations.

- One-hour initial consults are encouraged.
- For new and ongoing projects, an informal half-page summary of the project idea or status, and a description of assistance needed will be requested prior to the consult.
- Ongoing consults for different phases of the same project are encouraged.
- In-depth support involving more than several hours of support for a given phase requires prior approval.
- *Authorship.* Because the ARC typically provides intellectual contributions to projects, it is expected that the ARC be listed as a coauthor on products when appropriate.

Services Offered

Study Design
- Study design and project development
- Developing a testable research hypothesis
- Quality improvement and research studies

Institutional Review Board (IRB)
- Determining if IRB review is needed
- Identification of the right forms
- Review of applications and modifications

Study Infrastructure & Support
- Input into developing study protocols
- Facilitate getting student/volunteer help

Data Collection
- Input on surveys and data collection tools
- REDCap database support
  - REDCap is a tool that facilitates data entry of data collected from study participants (eg, survey)

Statistical Analysis
- Assist with statistical analysis plan
- Basic power calculations
- Guide biostatistics consultations
- Guide data cleaning for statistical analysis
- Conduct statistical analyses*

Products: Abstracts, Posters, Presentations, Manuscripts
- Provide review and input
- Particular focus on methods section

Resource identification and Support
- Identify training opportunities
- Field requests for small research resources*
  - Software, Amalga datasets, etc.

*These services require prior approval by GIM Leadership.

Contact Information:

[Name / Address or ARC]

FIG 1. Academic Research Coach Services and Consultations

Project Title

title / brief title description of what you are doing

Investigators, collaborators, authors

names and roles/expertise

Deliverables

(eg, journal articles [target journal, word limit], conference poster/presentation, preliminary data for grant)

Significance, Rationale, Background

Aims and Hypotheses
- General Aim
- Hypotheses, primary and secondary

Methods

Study Design
- Study Design: examples – cohort, cross-sectional study, pre-/post, unsure

Study Populations(s)
- Source population: clinic, time period, participants (eg, patients, providers), age, sex, condition
- Inclusions and exclusions

Data Collection
- How you will collect your data: survey, electronic, chart review
- Conceptual framework needed?
- Variables you want to collect data on, concepts that are important

Analysis and Tables
- Number of participants anticipated, if known
- What do you want to show/report
- Type of analysis you want to do, if known (eg, ttest, descriptive, statistical model, unsure)

Anticipated issues/challenges
- Key data you don't have but should, missing data
- Timing of data collection, lack of comparison, access to data, other, funds to do work

Institutional Review Board
- Do you need IRB? Is it research, quality/improvement, unsure?
- What IRBs are involved and what IRB forms (research, exempt, minimal risk, full review, unsure)

Funding and Timeline
- Cost and funds available, if any
- Brief summary of expected timeline

FIG 2. Project Planner

availability. In addition, the coach coordinated with the director of the Division's faculty development program to cohost works-in-progress seminars, identify coach clients to present at these meetings, and provide brief presentations on a basic research skill at meetings. Faculty built rapport with the coach through these activities and became more comfortable reaching out for assistance. Because of the large size of the Division, it was decided to roll out the initiative in a stepwise fashion, starting with hospitalists before expanding to the rest of the Division.

Most faculty contacted the coach by e-mail to request a consultation, at which time the coach requested that they complete a preconsultation handout (Figure 2). Initial coaching appointments lasted one hour and were in-person. Coaching entailed an in-depth analysis of the project plan and advice on how to move the project forward. The coach provided tailored scholarly project advice and expertise in research methods. After initial consultations, she would review grant proposals, IRB applications, manuscripts, case report forms, abstracts, and other products. Her efforts typically focused on improving the methods and scientific and technical writing. Assistance with statistical analysis was provided on a case-by-case basis to maintain broad availability. To address statistically complex questions, the coach had five hours of monthly access to a PhD biostatistician via an on-campus consulting service. Follow-up appointments were encouraged and provided as needed by e-mail, phone, or in-person. The coach conducted regular reach outs to facilitate projects. However, execution of the research was generally the responsibility of the faculty member.

Program Evaluation

To characterize the reach and scope of the program, the coach tracked the number of faculty supported, types of services provided, status of initiated projects, numbers of grants generated, and the dissemination of scholarly products including papers and abstracts. We used these metrics to create summary reports to identify successes and areas for improvement. Monthly meetings between the coach and Division leadership were used to fine-tune the approach.

We surveyed coach clients anonymously to assess their satisfaction with the coach initiative. Using Likert scale questions where 1 = completely disagree and 5 = completely agree, we asked (1) if they would recommend the coach to colleagues, (2) if their work was higher quality because of the coach, (3) if they were overall satisfied with the coach, (4) whether the Division should continue to support the coach, and (5) if the coach's lack of clinical training negatively affected their experience. This work was considered a quality improvement initiative for which IRB approval was not required.

RESULTS

Over 18 months, the coach supported a 49 Division members including 30 hospitalists and 63 projects. Projects included a wide range of scholarship: medical education research, qualitative research, clinical quality improvement projects, observational studies, and a randomized clinical trial. Many clients (n = 16) used the coach for more than one project. The scope of work included limited support projects (identifying research resource and brainstorming project feasibility) lasting one to two sessions (n = 25), projects with a limited scope (collegial reviews of manuscripts and assistance with IRB submissions) but requiring more than two consultations (n = 24), and ongoing in-depth support projects (contributions on design, data collection, analysis, and manuscript writing) that required three consultations or more (n = 14). The majority of Division members (75%) supported did not have master's level training in a health services-related area, six had NIH or other national-level funding, and two had small grants funded by local sources prior to providing support. The number of Division faculty on a given project ranged from one to four.

The coach directly supported 13 manuscripts with coach authorship, seven manuscripts without authorship, 11 abstracts, and four grant submissions (Appendix). The coach was a coauthor on all the abstracts and a coinvestigator on the grant applications. Of the 13 publications the coach coauthored, 11 publications have been accepted to peer-reviewed journals and two are currently in the submission process. The types of articles published included one medical evaluation report, one qualitative study, one randomized clinical trial, three quality assessment/improvement reports, and five epidemiologic studies. The types of abstracts included one qualitative report, one systematic review, one randomized clinical trial, two quality improvement projects, two epidemiologic studies, and four medical education projects. Three of four small grants submitted to local and national funders were funded.

The coach's influence extended beyond the Division. Forty-eight university faculty, fellows, or students not affiliated with general internal medicine benefited from coach coaching: 26 were authors on papers and/or abstracts coauthored by the coach, 17 on manuscripts the coach reviewed without authorship, and five participated in consultations.

The coach found the experience rewarding. She enjoyed working on the methodologic aspects of projects and benefited from being included as coauthor on papers.

Twenty-nine of the 43 faculty (67%) still at the institution responded to the program assessment survey. Faculty strongly agreed that they would recommend the coach to colleagues (average ± standard deviation [SD]: 4.7 ± 0.5), that it improved the quality of their work (4.5 ± 0.9), that they were overall satisfied with the coaching (4.6 ± 0.7), and that the Division should continue to support the coach (4.9 ± 0.4). Faculty did not agree that the lack of clinical training of the coach was a barrier (2.0 ± 1.3).

DISCUSSION

The coach program was highly utilized, well regarded, and delivered substantial, tangible, and academic output. We anticipate the coach initiative will continue to be a valuable resource for our Division and could prove to be a valuable model for other institutions seeking to bolster the scholarly work of clinical academicians.

Several lessons emerged through the course of this project. First, we realized it is essential to select a coach who is both knowledgeable and approachable. We found that after meeting the coach, many faculty sought her help who otherwise would not have. An explicit, ongoing marketing strategy with regular contact with faculty at meetings was a key to receiving consult requests.

Second, the lack of a clinical background did not seem to hinder the coach's ability to coach clinicians. The coach acknowledged her lack of clinical experience and relied on clients to explain the clinical context of projects. We also learned that the coach's substantial experience with the logistics of research was invaluable. For example, the coach had substantial experience with the IRB process and her pre-reviews of IRB applications made for a short and relatively seamless experience navigating the IRB process. The coach also facilitated collaborations and leveraged existing resources at our institution. For example, for a qualitative research project, the coach helped identify a health services faculty member with this specific expertise, which led to a successful collaboration and publication. Although a more junior coach with less established qualifications may be helpful with research methods and with the research process, our endeavor suggests that having a more highly trained and experienced researcher was extremely valuable. Finally, we learned that for a Division of our size, the 0.50 FTE allotted to the coach is a minimum requirement. The coach spent approximately four hours a week on marketing, attending faculty meetings and conducting brief didactics, two hours per week on administration, and 14 hours per week on consultations. Faculty generally received support soon after their requests, but there were occasional wait times, which may have delayed some projects.

Academic leaders at our institution have noted the success of our coach initiative and have created a demand for coach services. We are exploring funding models that would allow for the expansion of coach services to other departments and divisions. We are in the initial stages of creating an Academic Scholarship Support Core under the supervision of the coach. Within this Core, we envision that various research support services will be triaged to staff with appropriate expertise; for example, a regulatory coordinator would review IRB applications while a mas-

ter's level statistician would conduct statistical analyses.

We have also transitioned to a new coach and have continued to experience success with the program. Our initial coach (author C.M.M.) obtained an NIH R01, a foundation grant, and took over a summer program that trains dental faculty in clinical research methods leaving insufficient time for coaching. Our new coach also has a PhD in epidemiology with NIH R01 funding but has more available FTE. Both of our coaches are graduates of our School of Public Health and institutions with such schools may have good access to the expertise needed. Nonclinical PhDs are often almost entirely reliant on grants, and some nongrant support is often attractive to these researchers. Additionally, PhDs who are junior or mid-career faculty that have the needed training are relatively affordable, particularly when the resource is made available to large number of faculty. For example, our first coach cost $48,000 a year for 50% FTE.

A limitation to our assessment of the coach initiative was the lack of pre- and postintervention metrics of scholarly productivity. We cannot definitively say that the Division's scholarly output has increased because of the coach. Nevertheless, we are confident that the coach's coaching has enhanced the scholarly work of individual clinicians and provided value to the Division as a whole. The coach program has been a success in our Division. Other institutions facing the challenge of supporting the research efforts of academic clinicians may consider this model as a worthy investment.

Disclosures: The authors have nothing to disclose.

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Nephrotoxin-Related Acute Kidney Injury and Predicting High-Risk Medication Combinations in the Hospitalized Child

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BACKGROUND: In the hospitalized patient, nephrotoxin exposure is one potentially modifiable risk factor for acute kidney injury (AKI). Clinical decision support based on nephrotoxin ordering was developed at our hospital to assist inpatient providers with the prevention or mitigation of nephrotoxin-related AKI. The initial decision support algorithm (Algorithm 1) was modified in order to align with a national AKI collaborative (Algorithm 2).

OBJECTIVE: Our first aim was to determine the impact of this alignment on the sensitivity and specificity of our nephrotoxin-related AKI detection system. Second, if the system efficacy was found to be suboptimal, we then sought to develop an improved model.

DESIGN: A retrospective cohort study in hospitalized patients between December 1, 2013 and November 30, 2015 (N = 14,779) was conducted.

INTERVENTIONS: With the goal of increasing nephrotoxin-related AKI detection sensitivity, a novel model based on the identification of combinations of high-risk medications was developed.

RESULTS: Application of the algorithms to our nephrotoxin use and AKI data resulted in sensitivities of 46.9% (Algorithm 1) and 43.3% (Algorithm 2, $P = .22$) and specificities of 73.6% and 89.3%, respectively ($P < .001$). Our novel AKI detection model was able to deliver a sensitivity of 74% and a specificity of 70%.

CONCLUSIONS: Modifications to our AKI detection system by adopting Algorithm 2, which included an expanded list of nephrotoxins and equally weighting each medication, did not improve our nephrotoxin-related AKI detection. It did improve our system's specificity. Sensitivity increased by >50% when we applied a novel algorithm based on observed data with identification of key medication combinations. *Journal of Hospital Medicine* 2019;14:462-467. Published online first April 8, 2019. © 2019 Society of Hospital Medicine

Acute kidney injury (AKI) is increasingly common in the hospitalized patient[1,2] with recent adult and pediatric multinational studies reporting AKI rates of 57% and 27%, respectively.[3,4] The development of AKI is associated with significant adverse outcomes including an increased risk of mortality.[5-7] For those that survive, the history of AKI may contribute to a lifetime of impaired health with chronic kidney disease.[8,9] This is particularly concerning for pediatric patients as AKI may impact morbidity for many decades, influence available therapies for these morbidities, and ultimately contribute to a shortened lifespan.[10]

AKI in the hospitalized patient is no longer accepted as an unfortunate and unavoidable consequence of illness or the indicated therapy. Currently, there is strong interest in this hospital-acquired condition with global initiatives aimed at increased prevention and early detection and treatment of AKI.[11,12] To this objective, risk stratification tools or prediction models could assist clinicians in decision making. Numerous studies have tested AKI prediction models either in particular high-risk populations or based on associated comorbidities, biomarkers, and critical illness scores. These studies are predominantly in adult populations, and few have been externally validated.[13] While associations between certain medications and AKI are well known, an AKI prediction model that is applicable to pediatric or adult populations and is based on medication exposure is difficult. However, there is a growing recognition of the potential to develop such a model using the electronic health record (EHR).[14]

In 2013, Seattle Children's Hospital (SCH) implemented a nephrotoxin and AKI detection system to assist in clinical decision making within the EHR. This system instituted the automatic ordering of serum creatinines to screen for AKI when the provider ordered three or more medications that were suspected to be nephrotoxic. Other clinical factors such as the diagnoses or preexisting conditions were not considered in the decision-tool algorithm. This original algorithm (Algorithm 1) was later modified and the list of suspected nephrotoxins was expanded (Table 1) in order to align with a national pediatric AKI collaborative (Algorithm 2). However, it was unclear whether the algorithm modification would improve AKI detection.

The present study had two objectives. The first was to evaluate the impact of the modifications on the sensitivity and specificity of our system. The second objective, if either the

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sensitivity or specificity was determined to be suboptimal, was to develop an improved model for nephrotoxin-related AKI detection. Having either the sensitivity or the specificity under 50% would be equivalent to or worse than a random guess, which we would consider unacceptable.

METHODS

Context

SCH is a tertiary care academic teaching hospital affiliated with the University of Washington School of Medicine, Harborview Medical Center, and the Seattle Cancer Care Alliance. The hospital has 371 licensed beds and approximately 18 medical subspecialty services.

Study Population

This was a retrospective cohort study examining all patients ages 0-21 years admitted to SCH between December 1, 2013 and November 30, 2015. The detection system was modified to align with the national pediatric AKI collaborative, Nephrotoxic Injury Negated by Just-in-Time Action (NINJA) in November 2014. Both acute care and intensive care patients were included (data not separated by location). Patients who had end-stage kidney disease and were receiving dialysis and patients who were evaluated in the emergency department without being admitted or admitted as observation status were excluded from analysis. Patients were also excluded if they did not have a baseline serum creatinine as defined below.

Study Measures

AKI is defined at SCH using the Kidney Disease: Improving Global Outcomes Stage 1 criteria as a guideline. The diagnosis of AKI is based on an increase in the baseline serum creatinine by 0.3 mg/dL or an increase in the serum creatinine by >1.5 times the baseline assuming the incoming creatinine is 0.5 mg/dL or higher. For our definition, the increase in serum creatinine needs to have occurred within a one-week timeframe and urine output is not a diagnostic criterion.[15] Baseline serum creatinine is defined as the lowest serum creatinine in the previous six months. Forty medications were classified as nephrotoxins based on previous analysis[16] and adapted for our institutional formulary.

Statistical Analysis

To evaluate the efficacy of our systems in detecting nephrotoxin-related AKI, the sensitivity and the specificity using both our original algorithm (Algorithm 1) and the modified algorithm (Algorithm 2) were generated on our complete data set. To test sensitivity, the proportion of AKI patients who would trigger alert using Algorithm 1 and then with Algorithm 2 was identified. Similarly, to test specificity, the proportion of non-AKI patients who did not trigger an alert by the surveillance systems was identified. The differences in sensitivity and specificity between the two algorithms were evaluated using two-sample tests of proportion.

The statistical method of Combinatorial Inference has been utilized in studies of cancer biology[17] and in genomics.[18] A variation of this approach was used in this study to identify the specific medication combinations most associated with AKI. First, all of the nephrotoxic medications and medication combinations that were prescribed during our study period were identified from a data set (ie, a training set) containing 75% of all encounters selected at random without replacement. Using this training set, the prevalence of each medication combination and the rate of AKI associated with each combination were identified. The predicted overall AKI risk of an individual medication is the average of all the AKI rates associated with each combination containing that specific medication. Also incorporated into the determination of the predicted AKI risk was the prevalence of that medication combination.

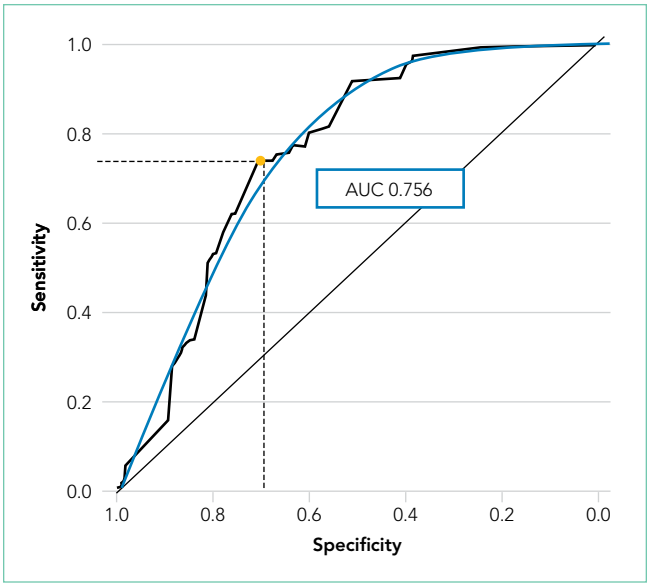

FIG. Receiver Operator Characteristic Curve for Acute Kidney Injury Prediction Model

To test our model's predictive capability, the algorithm was applied to the remaining 25% of the total patient data (ie, the test set). The predicted AKI risk was compared with the actual AKI rate in the test data set. Our model's predictive capability was represented in a receiver operator characteristic (ROC) analysis. The goal was to achieve an area under the ROC curve (AUC) approaching one as this would reflect 100% sensitivity and 100% specificity, whereas an AUC of 0.5 would represent a random guess (50% chance of being correct).

Lastly, our final step was to use our model's ROC curve to determine an optimal threshold of AKI risk for which to trigger an alert. This predicted risk threshold was based on our goal to increase our surveillance system's sensitivity balanced with maintaining an acceptable specificity.

An *a priori* threshold of $P = .05$ was used to determine statistical significance of all results. Analyses were conducted in Stata 12.1 (StataCorp LP, College Station, Texas) and R 3.3.2 (R Foundation for Statistical Computing, Vienna, Austria). A sample data set containing replication code for our model can be found in an online repository (https://dataverse.harvard.edu/dataverse/chuan). This study was approved by the Seattle Children's Institutional Review Board.

RESULTS

Sensitivity and Specificity

Of the patient encounters, 14,779 were eligible during the study period. The sensitivity of the system's ability to identify nephrotoxin-related AKI decreased from 46.9% using Algorithm 1 to 43.3% using Algorithm 2, a change of 3.6% ($P = .22$). The specificity increased from 73.6% to 89.3%, a change of 15.7% ($P < .001$; Table 2).

Improvement of Our Nephrotoxin-Related AKI Detection System Using a Novel AKI Prediction Strategy

A total of 838 medication combinations were identified in our training set and the predicted AKI risk for every medication combination was determined. By comparing the predicted risk of AKI to the actual AKI occurrence, an ROC curve with an AUC of 0.756 (Figure) was generated. An increase in system sensitivity was prioritized when determining the optimal AKI risk at which the model would trigger an alert. Setting an alert threshold at a predicted AKI risk of >8%, our model performed with a sensitivity of 74% while decreasing the specificity to 70%.

Identification of High-Risk Nephrotoxic Medications and Medication Combinations

Approximately 200 medication combinations were associated with >8% AKI risk, our new AKI prediction model's alert threshold. Medication combinations consisting of up to 11 concomitantly prescribed medications were present in our data set. However, many of these combinations were infrequently prescribed. Further analysis, conducted in order to increase the clinical relevance of our findings, identified 10 medications or medication combinations that were both associated with a predicted AKI risk of >8% and that were prescribed on average greater than twice a month (Table 3).

DISCUSSION

The nephrotoxin-related AKI detection system at SCH automatically places orders for serum creatinines on patients who have met criteria for concomitant nephrotoxin exposure. This has given us a robust database from which to develop our clinical decision-making tool. Both our original and updated systems were based on the absolute number of concomitant nephrotoxic medications prescribed.[16] This is a reasonable approach given the complexity of building a surveillance system[19] and resource limitations. However, a system based on observed rather than theoretical or *in vitro* data, adaptable to the institution and designed for ongoing refinement, would be more valuable.

The interest in AKI prediction tools continues to be high. Bedford et al. employed numerous variables and diagnostic codes to predict the development of AKI in adults during hospitalization. They were able to produce a prediction model with a reasonable fit (AUC 0.72) to identify patients at higher risk for AKI but were less successful in their attempts to predict progression to severe AKI.[20] Hodgson et al. recently developed an adult AKI prediction score (AUC 0.65-0.72) also based on numerous clinical factors that was able to positively impact

TABLE 1. **List of Suspected Nephrotoxins**

Acyclovir
Amikacin
Amphotericin B
Aspirin
Captopril
Carboplatin[a]
Ceftazidime[b]
Cidofovir
Cisplatin[a]
Colistimethate[b]
Cyclosporine
Enalapril
Enalaprilat
Foscarnet
Ganciclovir[b]
Gentamicin
Ibuprofen
Indomethacin
Ioversol
Ketorolac
Lisinopril
Losartan
Meloxicam
Mesalamine
Methotrexate
Mitomycin
Naproxen
Neomycin
Pamidronate
Pentamidine
Piperacillin[b]
Piperacillin-Tazobactam
Sirolimus[b]
Tacrolimus
Tenofovir
Ticarcillin/clavulanic acid[b]
Tobramycin
Valacyclovir[b]
Valganciclovir[b]
Valsartan
Vancomycin
Zoledronic acid

[a]Removed from monitoring list with Algorithm 2.
[b]Added to monitoring list with Algorithm 2.

TABLE 2. **Accuracy Measures of Acute Kidney Injury Alert System Using Algorithms 1 and 2**

		Algorithm 1		Algorithm 2	
True AKI Status	**Total**	**Alert**	**No Alert**	**Alert**	**No Alert**
Yes AKI	580	272 (46.9%[a])	308 (53.1%)	251 (43.3%[a])	329 (56.7%)
No AKI	14,199	3,744 (26.4%)	10,455 (73.6%[b])	1,517 (10.7%)	12,682 (89.3%[b])
Total	14,779	4016	10,763	1768	13,011

[a]Sensitivity = P (Alert = 1 | AKI = 1): 46.9% for Algorithm 1 vs 43.3% for Algorithm 2.
[b]Specificity = P (Alert = 0 | AKI = 0): 73.6% for Algorithm 1 vs 89.3% for Algorithm 2.
PPV = P (AKI = 1 | Alert = 1): 6.8% for Algorithm 1 vs 14.2% for Algorithm 2.
NPV = P (AKI = 0 | Alert = 0): 97.1% for Algorithm 1 vs 97.5% for Algorithm 2.
Abbreviations: AKI, acute kidney injury; NPV, negative predictive value; PPV, positive predictive value.

TABLE 3. **Frequently Prescribed Medications and Medication Combinations with a Predicted Acute Kidney Injury Risk of >8%**

Medication or Medication Combinations	**Percent Who Developed AKI**
Gentamicin + Piperacillin-Tazobactam + Vancomycin	23
Piperacillin-Tazobactam + Vancomycin	13
Enalapril	10
Acyclovir + Vancomycin	10
Piperacillin-Tazobactam	10
Cyclosporine	10
Vancomycin	9
Ceftazidime + Tobramycin	9
Ceftazidime + Vancomycin	8
Ibuprofen + Ioversol + Vancomycin	8

inpatient mortality.[21] To our knowledge, our model is unique in that it focuses on nephrotoxins using a predicted AKI risk algorithm based on observed AKI rates of previously ordered medications/medication combinations (2-11 medications). Having a decision tool targeting medications gives the clinician guidance that can be used to make a specific intervention rather than identifying a patient at risk due to a diagnosis code or other difficult to modify factors.

There are abundant case studies and reports using logistic regression models identifying specific medications associated with AKI. Our choice of methodology was based on our assessment that logistic regression models would be inadequate for the development of a real-time clinical decision-making tool for several reasons. Using logistic regression to explore every medication combination based on our medication list would be challenging as there are approximately 5.5×10^{10} potential medication combinations. Additionally, logistic regression ignores any potential interactions between the medications. This is an important point as medication interactions can be synergistic, neutral, or antagonist. Consequently, the outcome generated from a set of combined variables may be different from one generated from the sum of each variable taken independently. Logistic regression also does not account for the potential prescribing trends among providers as it assumes that all medications or medication combinations are equally available at the same time. However, in practice, depending on numerous factors, such as hospital culture (eg, the presence of clinical standard work pathways), local bacterial resistance patterns, or medication shortages; certain medication combinations may occur more frequently while others not at all. Finally, logistic regression cannot account for the possibility of a medication combination occurring; therefore, logistic regression may identify a combination strongly associated with AKI that is rarely prescribed.

We theorized that AKI detection would improve with the Algorithm 2 modifications, including the expanded nephrotoxin list, which accompanied alignment with the national pediatric AKI collaborative, NINJA. The finding that our surveillance sensitivity did not improve with this system update supported our subsequent objective to develop a novel nephrotoxin-related AKI decision tool or detection system using our EHR data to identify which specific medications and/or medication com-

binations were associated with a higher rate of AKI. However, it should be noted that two factors related to measurement bias introduce limitations to our sensitivity and specificity analyses. First, regarding the presence of the alert system, our system will order serum creatinines on patients when they have been exposed to nephrotoxins. Consequently, the proportion of patients with creatinines measured will increase in the nephrotoxin-exposed patients. Unexposed patients may have AKI that is not detected because creatinines may not be ordered. Therefore, there is the potential for a relative increase in AKI detection among nephrotoxin-exposed patients as compared with unexposed patients, which would then affect the measured sensitivity and specificity of the alert. Second, the automated alerts require a baseline creatinine in order to trigger therefore are unable to identify AKI among patients who do not have a baseline serum creatinine measurement.

Our new nephrotoxin-related AKI detection model performed best when an alert was triggered for those medications or medication combinations with a predicted AKI risk of >8%. Forty-six medication combinations consisting of exactly two medications were determined to have a predicted AKI risk of >8% therefore would trigger an alert in our new model system. These medication combinations would not have triggered an alert using either of the previous system algorithms as both algorithms are based on the presence of three or more concomitant nephrotoxic medications.

From the list of suspected nephrotoxins, we identified 11 unique medications in 10 different combinations with a predicted AKI risk of >8% that were prescribed frequently (at least twice a month on average; Table 3). Notably, six out of 10 medication combinations involved vancomycin. Piperacillin-tazobactam was also represented in several combinations. These findings support the concern that others have reported regarding these two medications particularly when prescribed together.[22,23]

Interestingly, enalapril was identified as a higher-risk medication both alone and in combination with another medication. We do not suspect that enalapril carries a higher risk than other angiotensin-converting enzyme (ACE) inhibitors to increase a patient's serum creatinine. Rather, we suspect that in our hospitalized patients, this relatively short-acting ACE inhibitor is commonly used in several of our vulnerable populations such as in cardiac and bone marrow transplant patients.

The alert threshold of our model can be adjusted to increase either the sensitivity or the specificity of AKI detection. Our detection sensitivity increased by >1.5-fold with the alert trigger threshold set at a predicted AKI risk of >8%. As a screening tool, our alert limits could be set such that our sensitivity would be greater; however, balancing the potential for alert fatigue is important in determining the acceptance and, ultimately, the success of a working surveillance system.[24]

A patient's overall risk of AKI is influenced by many factors such as the presence of underlying chronic comorbidities and the nature or severity of the acute illness as this may affect the patient's intravascular volume status, systemic blood pressures, or drug metabolism. Our study is limited as we are a children's hospital and our patients may have fewer comorbidities than seen in the adult population. One could argue that this permits a perspective not clouded by the confounders of chronic disease and allows for the effect of the medications prescribed to be more apparent. However, our study includes critically ill patients and patients who may have been hemodynamically unstable. This may explain why the NINJA algorithm did not improve the sensitivity of our AKI detection as the NINJA collaborative excludes critically ill patients.

Dose and dosing frequency of the prescribed medications could not be taken into account, which could explain the finding that nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, or ketorolac when used alone were associated with a low (<1%) rate of AKI despite being frequently prescribed. Additionally, as many providers are aware of the AKI risk of NSAIDs, these medications may have been used intermittently (as needed) or in select, perhaps healthier, patients or in patients that take these medications chronically who were admitted for reasons that did not alter their outpatient medication regimen.

Our study also reflects the prescribing habits of our institution and may not be directly applicable to nontertiary care hospitals or centers that do not have large cystic fibrosis, bone marrow, or solid organ transplant populations. Despite our study's limitations, we feel that there are several findings that are relevant across centers and populations. Our data were derived from the systematic ordering of daily serum creatinines when a patient is at risk for nephrotoxin-related AKI. This is in step with the philosophy advocated by others that AKI identification can only occur if the providers are aware of this risk and are vigilant.[25] In this vigilance, we also recognize that not all risks are of the same magnitude and may not deserve the same attention when resources are limited. Our identification of those medication combinations most associated with AKI at our institution has helped us narrow our focus and identify specific areas of potential education and intervention. The specific combinations identified may also be relevant to similar institutions serving similarly complex patients. Those with dissimilar populations could use this methodology to identify those medication combinations most relevant for their patient population and their prescriber's habits. More studies of this type would be beneficial to the medical community as a whole as certain medication combinations may be found to be high risk regardless of the institution and the age or demographics of the populations they serve.

Acknowledgments

Dr. Karyn E. Yonekawa conceptualized and designed the study, directed the data analysis, interpreted the data, drafted, revised and gave final approval of the manuscript. Dr. Chuan Zhou contributed to the study design, acquired data, conducted the data analysis, critically reviewed, and gave final approval of the manuscript. Ms. Wren L. Haaland contributed to the study design, acquired data, conducted the data analysis, critically reviewed, and gave final approval of the manuscript. Dr. Davene R. Wright contributed to the study design, data anal-

ysis, critically reviewed, revised, and gave final approval of the manuscript.

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All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Disclosures: The authors have no conflicts of interest to report.

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How Much Time are Physicians and Nurses Spending Together at the Patient Bedside?

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BACKGROUND: Bedside rounding involving both nurses and physicians has numerous benefits for patients and staff. However, precise quantitative data on the current extent of physician–nurse (MD–RN) overlap at the patient bedside are lacking.

OBJECTIVE: This study aimed to examine the frequency of nurse and physician overlap at the patient beside and what factors affect this frequency.

DESIGN: This is a prospective, observational study of time-motion data generated from wearable radio frequency identification (RFID)-based locator technology.

SETTING: Single-institution academic hospital.

MEASUREMENTS: The length of physician rounds, frequency of rounds that include nurses simultaneously at the bedside, and length of MD–RN overlap were measured and analyzed by ward, day of week, and distance between patient room and nursing station.

RESULTS: A total of 739 MD rounding events were captured over 90 consecutive days. Of these events, 267 took place in single-bed patient rooms. The frequency of MD–RN overlap was 30.0%, and there was no statistical difference between the three wards studied. Overall, the average length of all MD rounds was 7.31 ± 0.58 minutes, but rounding involving a bedside nurse lasted longer than rounds with MDs alone (9.56 vs 5.68 minutes, $P < .05$). There was no difference in either the length of rounds or the frequency of MD–RN overlap between weekdays and weekends. Finally, patient rooms located farther away from the nursing station had a lower likelihood of MD–RN overlap (Pearson's r = –0.67, $P < .05$).

CONCLUSION: RFID-based technology provides precise, automated, and high-throughput time-motion data to capture nurse and physician activity. At our institution, 30.0% of rounds involve a bedside nurse, highlighting a potential barrier to bedside interdisciplinary rounding. *Journal of Hospital Medicine* 2019;14:468-473. Published online first May 10, 2019. © 2019 Society of Hospital Medicine

Effective communication between physicians and nurses is an essential element of any healthcare system. Numerous studies have highlighted the benefits of high quality physician–nurse (MD–RN) communication, including improved patient outcomes,[1] higher patient satisfaction,[2] and better nurse job satisfaction and retention rates.[3-5] Having physicians and nurses round together (bedside interdisciplinary rounding) has been shown to improve the perception of teamwork,[6,7] reduce the number of pages for the physician team,[6,8] better involve the patients in developing the plan of care,[8] and even decrease the length and cost of stay.[9]

Being physically in the same space at the same time is the first and nonnegotiable requirement of bedside interdisciplinary rounding. However, precise and objective data regarding the extent to which physicians and nurses overlap at the patient bedside are lacking. Studies that examine the face-to-face component of MD–RN communication have generally relied on either qualitative methods, such as focus groups and surveys,[10,11] or quantitative methods that are subjective, such as validated scales.[12] In addition, the few studies that report quantitative data usually rely on manual observation methods that can be affected by various forms of observer bias.[10,13,14] There is also a paucity of data on how bedside overlap changes over the work week or as a function of room location.

Recently, real-time locator systems using radio frequency identification (RFID) have allowed measurement of staff and equipment movement in a precise and quantitative manner.[9,15] Although there have been previous studies using RFID locators to create time-motion maps of various hospital staff, no study has used RFID to measure and analyze the workflow of both physicians and nurses simultaneously.[16-18] The purpose of our investigation was to utilize our hospital-wide RFID staff locator technology to accurately and quantitatively assess physician and nurse rounding habits. Understanding the current

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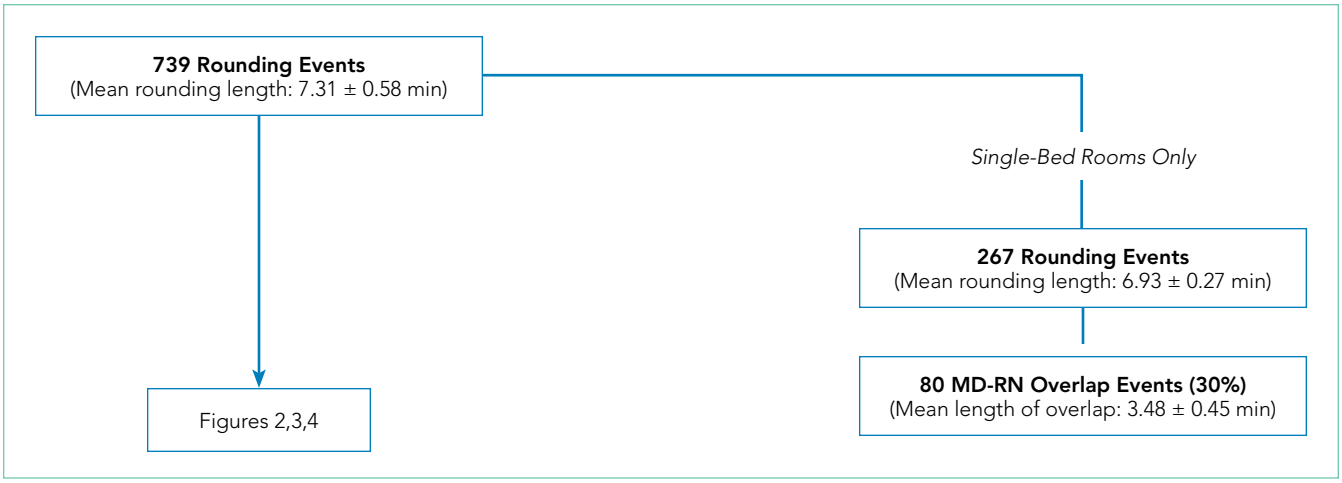

FIG 1. Baseline Overlap Frequency
Over 90 consecutive days, 739 MD rounding events were recorded. To analyze the frequency of MD rounds that overlapped with a bedside nurse, only the single-bed patient rooms were examined to reduce false positive overlap. Of the 267 events that took place in single-bed rooms, 80 involved a bedside nurse, for a MD-RN overlap rate of 30.0%. Lengths of time are shown ± SEM.

rate of overlap is an important first step to establishing bedside interdisciplinary rounding.

METHODS

Setting and Participants

The investigation was conducted at a single quaternary-care academic center. The study is exempt per our Institutional Review Board. Data were gathered from three adjacent medical-surgical acute care wards. The layout for each ward was the same: 19 single- or double-occupancy patient rooms arranged in a linear hallway, with a nursing station located at the center of the ward.

The study utilized wearable RFID tags (manufactured by Hill-Rom Holdings, Inc) that located specific staff within the hospital in real time. The RFID tags were checked at Hill-Rom graphical stations to ensure that their locations were tracked accurately. The investigators also wore them and walked around the wards in a prescripted manner to ensure validity. In addition, the locator accuracy was audited by participating attendings once per week and cross-checked with the generated data. Attending physicians on the University Hospitalist inpatient medicine teams were then given their uniquely-tagged RFIDs at the beginning of this study. Nurses already wear individual RFID tags as part of their normal standard-of-care workflow.

The attending hospitalists wore their RFID tags when they were on service for the entirety of the shift. They were encouraged to include nurses at the bedside, but this was not mandatory. The rounding team also included residents and medical students. Rounding usually begins at a prespecified time, but the route taken varies daily depending on patient location. Afternoon rounds were done as needed, depending on patient acuity. The attending physicians' participation in this study was not disclosed to the patient. The patient care activities and daily routines of both nurses and physicians were otherwise unaltered.

Study Design and Data Collection

Data were collected on the three wards for 90 consecutive days, including nights and weekends. As physicians and nurses moved throughout the ward to conduct their usual patient care activities, the temporal-spatial data associated with their unique RFIDs were automatically collected in real time by the Hill-Rom receivers built into each patient room. Every day, a spreadsheet detailing the activity of all participating nurses and physicians for the past 24 hours was generated for the investigators.

A rounding event was defined as any episode in which a physician was in a patient room for more than 10 seconds. Incidences in which a physician entered and left a room multiple times over a short time span (with less than five minutes in between each event) were classified as a single rounding event. A physician and a nurse were defined as having overlapped if their RFID data showed that they were in the same patient room for a minimum of 10 seconds at the same time. For the purposes of this study, data generated from other RFID-wearing professionals, such as nursing assistants or unit secretaries, as well as data collected from the hallways, were excluded.

Statistical Analysis

All statistical analyses were conducted using GraphPad Prism (GraphPad Software, San Diego, California). Rounding and overlap lengths were rounded to the nearest minute (minimum one minute). Mean lengths are expressed along with the standard error. Comparisons of the average lengths of MD rounding events between wards was conducted using two-tailed Student t-test or one-way ANOVA. Comparisons of the frequency of MD–RN overlap between wards and across different days of the week were performed using a Chi-squared test. The analysis of correlation between the frequency of MD–RN overlap and distance between patient room and nursing station was conducted by calculating Pearson's correlation. A *P* value of less than .05 was considered statistically significant.

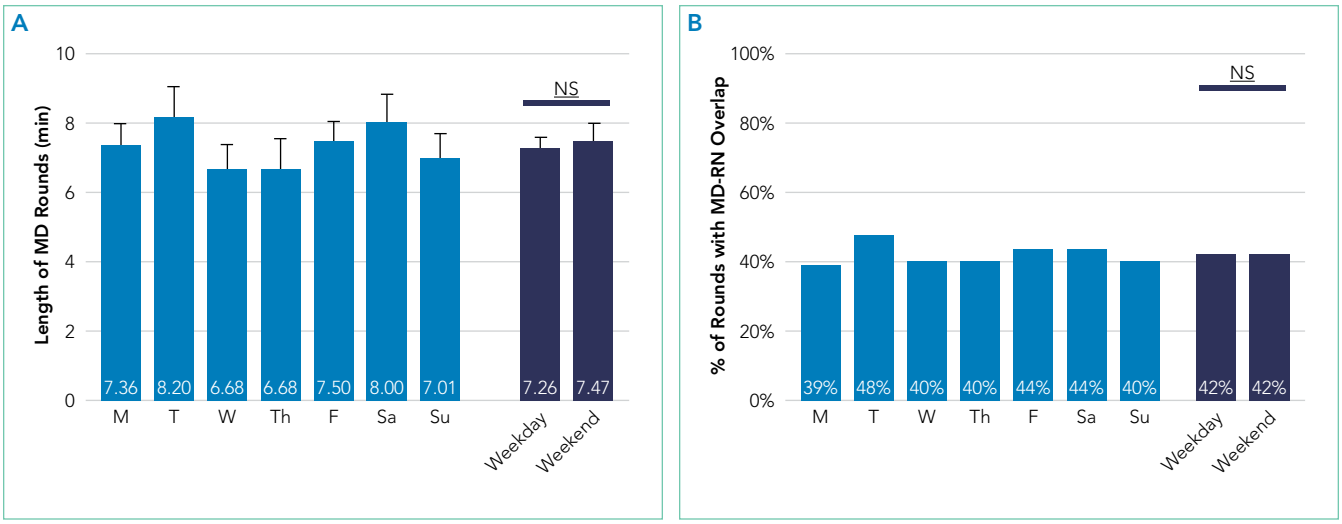

FIG 2. Rounding Characteristics by Day of Week

Data on the length of MD rounds and the frequency of MD-RN overlap for all rooms in the study were partitioned according to day of week. Monday through Friday data were then averaged as "Weekday" and Saturday and Sunday data were averaged as "Weekend." (A) Length of MD rounds by day of week. Mean rounding length in minutes are shown at the base of the bar graphs. Error bars represent standard error. (B) Frequency of MD-RN overlap by day of week. Frequencies of overlap are shown at the base of the bar graphs.

Abbreviation: NS; not statistically significant.

RESULTS

Baseline Rounding Characteristics

Over the study period of 90 consecutive days, 739 MD rounding events were captured, for an average of 8.2 events per day. The mean length of all MD rounding events was 7.31 minutes (±0.27, ranging from one to 70 minutes). Of these 739 MD rounding events, we separately examined the 267 events that took place in single-bed patient rooms, to control for false-positive physician and nurse interactions (for example, if the MD and RN were caring for two separate roommates). The average rounding length of single-bed rooms was 6.93 (±0.27) minutes (Figure 1). For the three individual wards, the average rounding lengths were 6.40 ± 0.73, 7.48 ± 0.94, and 7.02 ± 0.54 minutes, respectively (no statistically significant difference).

Frequency of MD–RN Overlap

Of the 267 MD rounding events observed in single-bed rooms, a nurse was present in the room for 80 events (30.0%). The frequencies of MD–RN overlap in patient rooms were 37.0% (30/81), 28.0% (14/50), and 26.5% (36/136) for the three individual wards ($P > .05$), respectively.

The *durations* of MD–RN overlap, when these events did occur, were 3.43 ± 0.38, 3.00 ± 0.70, and 3.69 ± 0.92 minutes, respectively ($P > .05$). The overall mean length of MD–RN overlap for all single rooms was 3.48 ± 0.45 minutes.

Rounding Characteristics over the Course of the Week

To assess how rounding characteristics differed over the work week, we partitioned our data into the individual days of the week. The length of each MD rounding event (time spent in each patient room) did not vary significantly over the course of the week (Figure 2a). When the data for the individual days were aggregated into "weekdays" (Monday through Friday) and "weekends" (Saturday and Sunday), the mean lengths of MD rounds were 7.26 ± 0.32 minutes on weekdays and 7.47 ± 0.52 minutes on weekends ($P > .05$).

In addition, there was no difference in how frequently physicians and nurses overlapped at the patient bedside between weekdays and weekends. Of the 565 weekday MD rounding events, 238 had a nurse at bedside (42.1%), and of the 173 weekend MD rounding events, 73 had a nurse at bedside (42.2%; Figure 2b).

Effect of a Bedside Nurse on the Length of Rounds

Next, the data on the length of MD rounds were partitioned based on whether there was a bedside nurse present during rounds. The mean length of rounds with only MDs (without a bedside nurse) was 5.68 ± 0.24 minutes. By comparison, the mean length of rounds with both a nurse and a physician at the patient bedside was 9.56 ± 0.53 minutes (Figure 3). This difference was statistically significant ($P < .001$).

Association between Patient Room Location and the Likelihood of MD–RN Overlap

All three wards in this study have a linear layout, consisting of 19 patient rooms in a row (Figure 4a). The nursing station is located in a central position within each ward, across from the 10th patient room. The frequency of MD–RN overlap was calculated for each room, and each room was ranked according to its relative distance from the nursing station. For each individual ward, there was no statistically significant trend in MD–RN overlap frequency as a function of the distance to the nursing station (data not shown). However, when the data from all three wards were aggregated, there was a statistically significant trend ($P < .05$) with a negative Pearson correlation

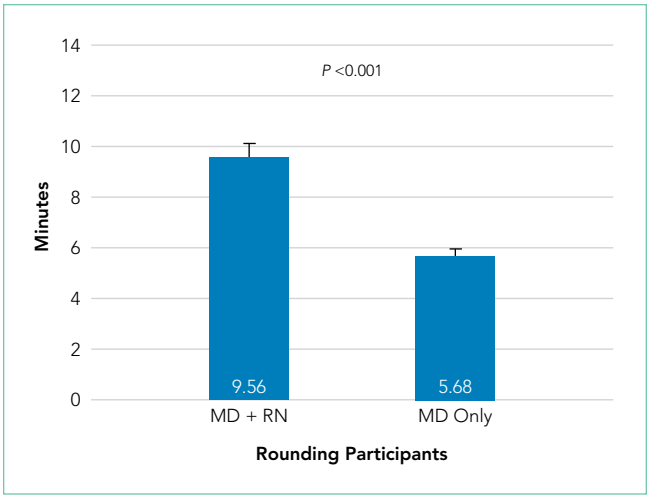

FIG 3. Effect of Bedside Nurse on Rounding Length
All rounding events were characterized into two groups: those with only the hospitalist attending's team (MD Only), and those that included a bedside nurse (MD + RN). The mean rounding length in minutes for each group are shown at the base of the bar graphs. Error bars represent standard error. A two-tailed student t-test was used to compare the mean rounding lengths.

(r = –0.670; Figure 4b). The slope of the best fit line was 1.94, suggesting that for each additional room farther away from the nursing station, the likelihood of interdisciplinary rounds (with both physicians and nurses together at the bedside) decreases by almost 2%.

DISCUSSION

To the best of our knowledge, this is the first time-motion study of MD–RN overlap using real-time, RFID-based location technology to capture the rounding activity of both nurses and physicians. Our primary interest was to examine the extent of MD–RN overlap at the patient bedside. This is an important metric that can pave the way for bedside interdisciplinary rounds. Although the exact nature of nurse-physician communication was not measured using the methodology in this study, understanding the length of time physicians spend in patient rooms, across different wards and throughout the work week, provides insights on the current workflow and potential areas of improvement. For example, we found that 30.0% of MD rounds overlapped with a nurse at the bedside. This baseline data highlight one potential barrier to institution-wide bedside interdisciplinary rounds. Workflow changes, such as better co-localization of patients by service lines or utilization of technologies to augment the visibility of rounding physicians, may improve this overlap frequency.

Data in the literature regarding how much interaction physicians and nurses have, especially at the bedside, are sparse and vary widely. In a recent study using medical students as observers by Stickrath et al., 807 MD rounding events led by medicine attendings were observed over 90 days. The frequency of rounding events that included "communication with nurse" was only 12%.[19] Furthermore, only 64.9% of these communications were *at the bedside*, for an effective prevalence of bedside MD–RN communication of 7.8%. This number is low compared to our observed frequency of 30.0%. On the other extreme, a study from a hospital that intentionally institutes multidisciplinary rounding (explicitly defined as involving a physician and a nurse at a bedside) reported a frequency range of 63% to 81%.[7] A follow-up study by the same group again demonstrated a high frequency of multidisciplinary rounds (74%) across a variety of ward and specialty types (range 35% to 97%.).[11] However, because of the selection bias of this particular setting, the high prevalence does not reflect a generalizable frequency of bedside MD–RN overlap at most hospitals.

The length of time spent by physicians at the patient bedside balances the competing demands of patient care and rapport-building with maintaining efficiency and progressing to other important tasks. In our study, physicians spent an av-

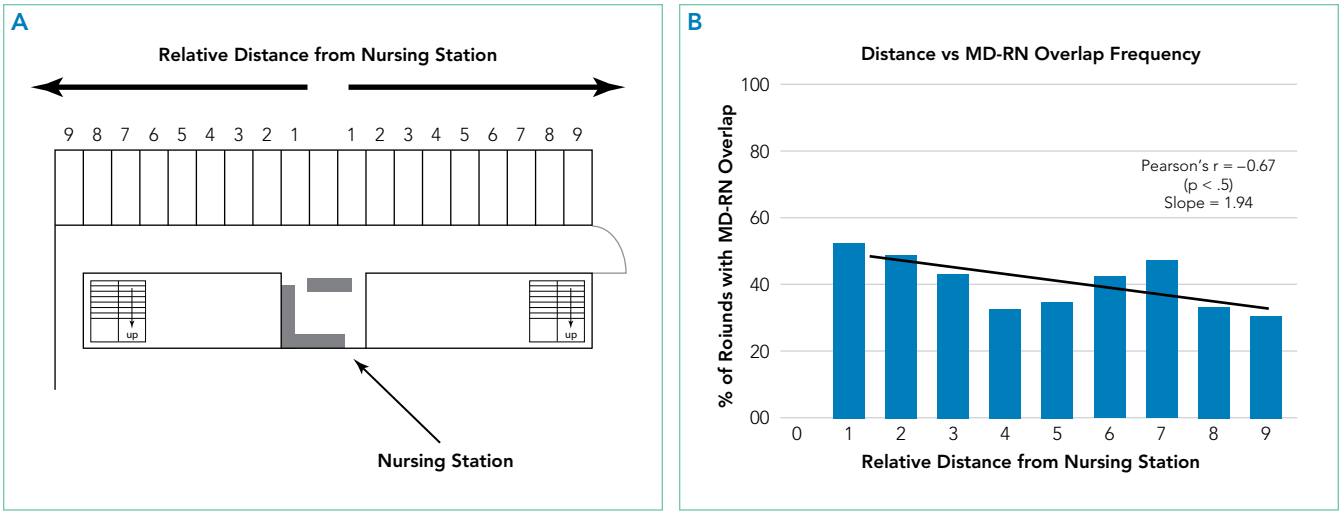

FIG 4. Room Location Affects Likelihood of Interdisciplinary RoundsData on the Frequency of MD-RN Overlap at the Bedside.
Data were analyzed for each patient room, and each patient room was then ranked according to its relative distance from the central nursing station. (A) Schematic layout of the inpatient ward. 19 patient rooms are arranged in a linear hallway, with a nursing station in the center of the ward. (B) Frequency of MD-RN overlap is shown for each group of rooms arranged by their distance from the nursing station. The solid line represents the best-fit line (slope), with a value of -1.94.

erage of 7.31 minutes at the bedside per patient. A previously published multiinstitutional observational study, which included our hospital, reported that the average length of rounds at bedside was 4.8 minutes.[13] A second study reported that 8.0 minutes were spent at the bedside per patient.[7] All three studies examined the same setting of internal medicine rounds at academic university-based hospitals, led by an attending physician with junior and senior residents present. However, the methodologies to measure the length of physician rounds were different: Priest et al. involved observers, Gonzalos et al. used E-mail-based surveys, and we utilized RFID-based locators. Additional institutional, individual, and patient-based factors also influence the length of rounds and are challenging to directly measure.

Furthermore, the discovery that the length of rounds and the frequency of MD–RN overlap did not statistically differ between weekdays and weekends ($P > .05$) was unexpected. Given the general trend of reduced physician staffing on weekends and the practice of cross-covering larger patient censuses, we would have expected shorter rounds and less frequent MD–RN overlap on the weekends.[7,20] The remarkable similarity between weekday and weekend metrics suggests that our workflow and rounding habits are not compromised on the weekends.

In addition, we found that MD rounds with a nurse at bedside took longer than rounds without a nurse, and that patient rooms located farther away from the central nursing station had a lower frequency of MD–RN overlap. However, we want to emphasize that these findings are merely associative, and not causal. For example, sicker patients usually take longer to round on than stable patients, and it is also the sicker patients who are more likely to have their nurses at the bedside, independent of physician rounding activity. Furthermore, even if rounding with nurses takes more time, it may ultimately result in fewer pages and overall time savings for both physicians and nurses.[6]

With regards to the association between room location and frequency of MD–RN overlap, the data can be interpreted in two ways. On the one hand, if the distance between the patient room and the nursing station does, in fact, reduce the frequency of overlap by almost 2% per room (Figure 4b), these data can be informative for future workflow development, quality improvement projects, or even hospital design. On the other hand, many wards might intentionally place more stable, less acute patients farther away from the nursing station because they do not need to be watched as closely. In that case, these data confirm their expectations and no action is needed.

There are several limitations to our study. The principal limitation, as discussed above, is that while our RFID system can generate large quantities of precise data on MD–RN overlap, we do not know the qualitative nature of the overlap. Just because a nurse and a physician are in the same room at the same time does not mean that they are communicating with each other. Second, we defined "rounding" as lasting a minimum of 10 seconds at the bedside. We believe that at least 10 seconds is needed to engage in any meaningful interaction between the physician and the patient, or the physician and the nurse. Reducing the time cutoff below 10 seconds risks capturing more "noise," (decreasing specificity) whereas increasing the time cutoff above 10 seconds risks losing out on encounters that actually had substantial communication (decreasing sensitivity). Even if the communications can be classified as pure "social check-ins," we believe these are important data to capture, as social check-ins are an important part of the patient's care and experience. Third, several studies have commented on the modest accuracy of RFID technology as a locator system.[15,21] To address this, we both validated the accuracy of our RFID tags prior to the study and restricted our measurements to only inside patient rooms, which has less signal noise than hallways.

Future directions include expanding this study to include housestaff and physicians from other specialities, which may reveal different patterns and metrics of patient and nurse interactions.

CONCLUSION

RFID technology is a high-throughput method of generating precise, quantitative, and objective data on physician and nurse rounding habits. This tool can be widely applied to generate baseline rounding and overlap data for a variety of wards and settings, especially for institutions that are interested in comparing their metrics and performance to other peer wards or hospitals. Furthermore, this method can generate the necessary pre- and postintervention data for countless quality improvement endeavors, including efforts to enhance bedside interdisciplinary rounding.

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Disclosures: The authors have nothing to disclose.

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Discharge Medical Complexity, Change in Medical Complexity and Pediatric 30-day Readmission

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BACKGROUND: While medical complexity is associated with pediatric readmission risk, less is known about how increases in medical complexity during hospitalization affect readmission risk.

METHODS: We conducted a five-year retrospective, case-control study of pediatric hospitalizations at a tertiary care children's hospital. Cases with a 30-day unplanned readmission were matched to controls based on admission seasonality and distance from the hospital. Complexity variables included the number of medications prescribed at discharge, medical technology, and the need for home healthcare services. Change in medical complexity variables included new complex chronic conditions and new medical technology. We estimated odds of 30-day unplanned readmission using adjusted conditional logistic regression.

RESULTS: Of 41,422 eligible index hospitalizations, we included 595 case and 595 control hospitalizations. Complexity: Polypharmacy after discharge was common. In adjusted analyses, being discharged with ≥2 medications was associated with higher odds of readmission compared with being discharged without medication; children with ≥5 discharge medications had a greater than four-fold higher odds of readmission. Children assisted by technology had higher odds of readmission compared with children without technology assistance. Change in complexity: New diagnosis of a complex chronic condition (Adjusted Odds Ratio (AOR) = 1.75; 1.11-2.75) and new technology (AOR = 1.84; 1.09-3.10) were associated with higher risk of readmission when adjusting for patient characteristics. However, these associations were not statistically significant when adjusting for length of stay.

CONCLUSION: Polypharmacy and use of technology at discharge pose a substantial readmission risk for children. However, added technology and new complex chronic conditions do not increase risk when accounting for length of stay. *Journal of Hospital Medicine* 2019;14:474-481. © 2019 Society of Hospital Medicine

Hospitalizations are disruptive, stressful, and costly for patients and families.[1-5] Hospital readmissions subject families to the additional morbidity inherent to hospitalization and place patients at additional risk of hospital-acquired conditions or other harm.[6-9] In pediatrics, hospital readmissions are common for specific conditions;[10] with rates varying across institutions;[10,11] and as many as one-third of unplanned pediatric readmissions are potentially preventable.[12]

Reducing pediatric readmissions requires a deeper understanding of the mechanisms through which readmissions occur. Medical complexity—specifically chronic conditions and use of medical technology—is associated with increased risk of readmission.[13,14] Polypharmacy at discharge has also been associated with readmission.[15,16] However, prior studies on polypharmacy and readmission risk examined the count of total medications and did not consider the nuances of scheduled versus as-needed medications, or the frequency of doses. These nuances may be critical to caregivers as discharge medical complexity can be overwhelming, even in diagnoses which are not traditionally considered complex.[17] Finally, of potentially greater importance than medical complexity at discharge is a change in medical complexity during a hospitalization—for example, new diagnoses or new technologies that require additional education in hospital and management at home.

We sought to further understand the relationship between discharge medical complexity and readmission risk with re-

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gards to polypharmacy and home healthcare referrals at discharge. Specifically, we hypothesized that a change in medical complexity during an admission—ie, a new chronic diagnosis or new technology—would be a more prominent risk factor for readmission than discharge complexity alone. We examined these factors in the context of length of stay (LOS) since this is a marker of in-hospital severity of illness and a potentially modifiable function of time allowed for in-hospital teaching and discharge preparation.

METHODS

We conducted a retrospective, case-control study of pediatric hospitalizations at one tertiary care children's hospital. Children <18 years were eligible for inclusion. Normal birth hospitalizations were excluded. We randomly selected one hospitalization from each child as the index visit. We identified cases, hospitalizations at C.S. Mott Children's Hospital between 2008 and 2012 with a subsequent unplanned 30-day readmission,[18] and matched them one to one with hospitalizations at the same hospital during the same period without subsequent readmission. We matched cases to controls based on the month of admission to account for seasonality of certain illnesses. We also matched on distance and direction from the hospital to the patient's home to account for the potential to have readmissions to other institutions. We utilized both distance and direction recognizing that a family living 30 miles in one direction would be closer to an urban area with access to more facilities, as opposed to 30 miles in another direction in a rural area without additional access. We subsequently performed medical record review to abstract relevant covariates.

Primary Predictors

Medical Complexity Models (Models 1 and 2):

We evaluated three attributes of discharge medical complexity abstracted by medical record review—discharge medications, technology assistance (ie, tracheostomy, cerebral spinal fluid ventricular shunt, enteral feeding tube, central line), and the need for home healthcare after discharge. We counted discharge medications based on the number of medications listed on the discharge summary separated into scheduled or as needed.[19] We also considered the number of scheduled doses to be administered in a 24-hour period (see Appendix methods for more information on counting discharge medications). For assistance by technology, we considered the presence of tracheostomy, cerebral spinal fluid ventricular shunt, enteral feeding tube, and central lines. While we describe these technologies separately, for multivariable analyses we considered the presence of any of the four types of technology.

Change in Medical Complexity Models (Models 3 and 4)

We examined two aspects of change in medical complexity—the presence of a new complex chronic condition (CCC)[20] diagnosed during the hospitalization, and a new reliance on medical technology. The presence of new CCC was determined by comparing discharge diagnoses to past medical history abstracted by medical record review. A new CCC was defined as any complex chronic condition that was captured in the discharge diagnoses but was not evident in the past medical history. By definition, all CCCs coded during birth hospitalization (eg, at discharge from the neonatal intensive care unit) were assigned to "new" CCC. We calculated a kappa statistic to determine interrater reliability in determining the designation of new CCC. A sensitivity analysis examining these birth CCCs was also performed comparing no new CCC, new CCC, and new CCC after birth hospitalization. The methods appendix provides additional information on considering new CCCs. New technology, abstracted from chart review, was defined as technology placed during hospitalization that remained in place at discharge. If a child with existing technology had additional technology placed during the hospitalization (eg, a new tracheostomy in a child with a previously placed enteral feeding tube), the encounter was considered as having new technology placed.

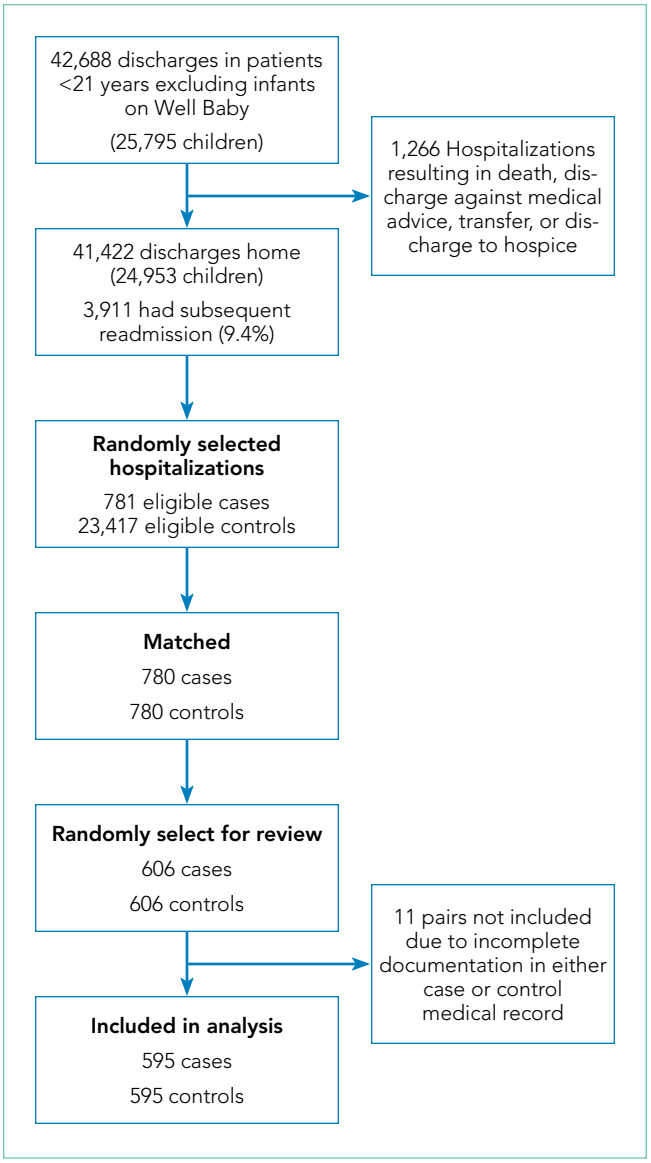

FIG. Cohort Derivation

TABLE 1. **Patient Characteristics and Frequency of Medical Complexity**

			Hospitalizations with Subsequent 30-day Readmission	Hospitalizations without Subsequent 30-day Readmission
			Cases (n = 595) Number (column %)	Controls (n = 595) Number (column %)
Patient/ Hospitalization Characteristics	Age	Newborn birth	20 (3.4)	34 (5.7)
		≤1 year, non-newborn	105 (17.7)	121 (20.3)
		>1 to ≤5	105 (17.7)	114 (19.2)
		>5 to ≤10	123 (20.7)	90 (15.1)
		>10 ≤15	108 (18.2)	118 (19.8)
		>15 years	134 (22.5)	118 (19.8)
	Race/ethnicity	Non-Hispanic White	443 (74.5)	458 (77.0)
		Non-Hispanic Black	73 (12.3)	66 (11.1)
		Hispanic or another race	62 (10.4)	46 (7.7)
		Unknown	17 (2.9)	25 (4.2)
	Gender	Female	286 (48.1)	276 (46.4)
	Insurance	Private	347 (58.3)	386 (64.9)
		Medicaid	160 (26.9)	164 (27.6)
		Funds for children with medical complexity	87 (14.6)	43 (7.2)
		Self-pay/other including Medicare	1 (0.2)	2 (0.3)
	Length of stay	0-1 days	96 (16.1)	208 (35.0)
		2-3 days	192 (32.3)	198 (33.3)
		4-5 days	86 (14.5)	82 (13.8)
		6-7 days	58 (9.8)	24 (4.0)
		7-14 days	82 (13.8)	40 (6.7)
		>14 days	81 (13.6)	43 (7.2)

Continued on page 477

Covariates

We created different sets of multivariable models to account for patient/hospitalization characteristics. In Models 1 and 3, we examined the primary predictors adjusting for patient characteristics (age, race/ethnicity, sex, and insurance). In Models 2 and 4, we added the index hospitalization LOS into the multivariable models adjusting for patient characteristics. We chose to add LOS in a second set of models because it is a potentially important confounder in readmission risk: discharge timing is a modifiable factor dependent on both physiologic recovery and the medical team's perception of caregiver's readiness for discharge. We elected to present models with and without LOS since LOS is also a marker of illness severity while in the hospital and is linked to discharge complexity.

Statistical Analysis

A review of 600 cases and 600 controls yields 89% power to detect statistical significance for covariates with an odds ratio of 1.25 ($\beta = 0.22$) if the candidate covariate has low to moderate correlation with other covariates (<0.3). If a candidate covariate has a moderate correlation with other covariates (0.6), we have 89% power to detect an odds ratio of 1.35 ($\beta = 0.30$).[21] We calculated odds of 30-days unplanned readmission using conditional logistic regression to account for matched case-control design. All the analyses were performed using STATA 13 (Stata Corp., College Station, Texas).

RESULTS

Of the 41,422 eligible index hospitalizations during the study period, 9.4% resulted in a 30-day unplanned readmission. Af-

TABLE 1. **Patient Characteristics and Frequency of Medical Complexity (continued)**

			Hospitalizations with Subsequent 30-day Readmission	Hospitalizations without Subsequent 30-day Readmission
			Cases (n = 595) Number (column %)	**Controls (n = 595)** Number (column %)
Medical Complexity at Index Discharge	Number of scheduled medications[a]	0	50 (8.4)	143 (24.0)
		1	82 (13.8)	142 (23.9)
		2	84 (14.1)	99 (16.6)
		3	66 (11.1)	79 (13.3)
		4	61 (10.3)	33 (5.6)
		5+	252 (42.4)	99 (16.6)
	Number of as-needed (prn) medications[b]	0	204 (34.3)	243 (40.8)
		1	177 (29.8)	169 (28.4)
		2	94 (15.8)	85 (14.3)
		3	75 (12.6)	65 (10.9)
		4	29 (4.9)	21 (3.5)
		5+	16 (2.7)	12 (2.0)
	Number of scheduled doses per 24 hours	Median (IQR)	6 (3,12)	3 (0,7)
	Medical technology	Any	249 (41.9)	85 (14.3)
	Specific types of medical technology	Tracheostomy	19 (3.2)	8 (1.3)
		Ventricular shunt	29 (4.9)	11 (1.9)
		Surgically placed enteral tube	66 (11.1)	19 (3.2)
		Nonsurgically placed enteral tube	44 (7.4)	30 (5.0)
		Central line	158 (26.6)	26 (4.4)
	Home healthcare after discharge		260 (43.7)	138 (23.2)
Change in Medical State Complexity	Any new complex chronic condition		105 (17.7)	60 (10.1)
	Any new technology		101 (17.0)	43 (7.2)

[a]Median (IQR) of number of scheduled medications: Cases—4 (2,7) Controls—2 (1, 3)
[b]Median (IQR) of number of prn medications: Cases—1 (0, 2) Controls—1 (0, 2)
Abbreviations: IQR, interquartile range; PRN, pro re nata (as needed).

ter randomly selecting one hospitalization per child, there were 781 eligible cases. We subsequent matched all but one eligible case to a control. We randomly selected encounters for medical record review, reviewing a total of 1,212 encounters. After excluding pairs with incomplete records, we included 595 cases and 595 controls in this analysis (Figure). Patient/hospitalization characteristics are displayed in Table 1. The most frequent primary discharge diagnoses are displayed in Appendix Table 1.

Models of Medical Complexity at Discharge

Polypharmacy after discharge was common for both readmitted and nonreadmitted patients. Children who experienced unplanned readmission in 30 days were discharged with a median of four different scheduled medications (interquartile range [IQR] 2,7) which translated into a median of six (IQR 3,12) scheduled doses in a 24-hour period. In comparison, children without an unplanned readmission had a median of two different scheduled medications (IQR 1,3) with a median of three (IQR 0,7) scheduled doses in a 24-hour period. Medical technology was more common in case children (42%) than in control children (14%). Central lines and enteral tubes were the most common forms of medical technology in both cases and controls. Home health referral was common in both cases (44%) and controls (23%; Table 1).

Many attributes of complexity were associated with an elevated readmission risk in bivariate analysis (Table 2). As the measures of scheduled polypharmacy (the number of sched-

TABLE 2. **Bivariate Logistic Regression Models**

			Odds Ratio (95% CI)
Medical Complexity at Index Discharge	Number of scheduled medications	0	REF
		1	1.70 (1.09-2.65)
		2	2.36 (1.50-3.72)
		3	2.62 (1.62-4.24)
		4	5.74 (3.25-10.14)
		5+	8.43 (5.36-13.25)
	Number of as needed (prn) medications	0	REF
		1	1.25 (0.94-1.64)
		2	1.34 (0.94-1.91)
		3	1.36 (0.93-2.01)
		4	1.67 (0.92-3.04)
		5+	1.62 (0.73-3.59)
	Number of scheduled doses per 24 hours		1.11 (1.08-1.13)
	Medical technology	Any	4.49 (3.27-6.16)
	Specific types of medical technology	Tracheostomy	2.57 (1.07-6.16)
		Ventricular shunt	2.80 (1.36-5.76)
		Surgically placed enteral tube	4.13 (2.35-7.26)
		Nonsurgically placed enteral tube	1.52 (0.93-2.47)
		Central line	7.60 (4.77-12.11)
	Home healthcare after discharge		2.77 (2.10-3.65)
Change in Medical Complexity	Any new complex chronic condition		1.94 (1.37-2.74)
	Any new technology		2.81 (1.88-4.21)

uled medications and number of doses per 24 hours) increased, the odds of readmission also increased in a dose-response manner. Higher numbers of as-needed medications did not increase the odds of readmission. Being assisted with any medical technology was associated with higher odds of readmission. Specifically, the presence of a central line had the highest odds of readmission in unadjusted analysis (odds ratio [OR] 7.60 (95% confidence interval [CI]: 4.77-12.11). In contrast, the presence of a nonsurgically placed enteral feeding tube (eg, nasogastric tube) was not associated with readmission. Finally, in unadjusted analyses, home healthcare need was associated with elevated odds of readmission.

In Model 1 (adjusting only for patient characteristics; Table 3), being discharged on two or more scheduled medications was associated with higher odds of readmission compared to being discharged without medications, with additional medications associated with even higher odds of readmission. Children with any technology had higher odds of readmission than children without medical technology. Likewise, home healthcare visits after discharge were associated with elevated odds of readmission in multivariable analyses without LOS. However, after adding LOS to the model (Model 2), home healthcare visits were no longer significantly associated with readmission.

Change in Medical Complexity Models

The adjudication of new CCCs had good reliability (K = 0.72). New CCCs occurred in 18% and new technologies occurred in 17% of cases. Comparatively, new CCCs occurred in 10% and new technologies in 7% of hospitalizations in control children (Table 1). In bivariate analyses, both aspects of change in medical complexity were associated with higher odds of readmission (Table 2). In multivariate analysis with patient characteristics (Model 3; Table 3), all aspects of change in complexity were associated with elevated odds of readmission. A new CCC was associated with higher odds of readmission (adjusted OR (AOR) 1.75, 95% CI: 1.11-2.75) as was new technology during admission (AOR 1.84, 95%CI: 1.09-3.10). Furthermore, the odds of readmission for medical complexity variables

TABLE 3. **Multivariable Logistic Regression models**[a]

			Model 1: Complexity Model Adjusted for Patient Demographics Adjusted Odds Ratio (95%CI)	Model 2: Complexity Model Adjusted for Patient Demographics and LOS Adjusted Odds Ratio (95%CI)	Model 3: Change in Complexity Adjusted for Patient Demographics Adjusted Odds Ratio (95%CI)	Model 4: Change in Complexity Adjusted for Patient Demographics and LOS Adjusted Odds Ratio (95%CI)
Medical Complexity at Index Discharge	Number of scheduled medications	0	REF	REF	REF	REF
		1	1.39 (0.86-2.22)	1.23 (0.75-2.01)	1.34 (0.83-2.15)	1.20 (0.73-1.98)
		2	**2.13 (1.30-3.50)**	**1.97 (1.17-3.32)**	**2.10 (1.27-3.46)**	**1.98 (1.17-3.36)**
		3	**1.86 (1.09-3.16)**	**1.81 (1.03-3.18)**	**1.86 (1.09-3.18)**	**1.83 (1.04-3.22)**
		4	**3.78 (2.00-7.14)**	**3.58 (1.81-7.09)**	**3.61 (1.89-6.89)**	**3.33 (1.67-6.66)**
		5+	**4.99 (2.99-8.35)**	**4.63 (2.69-7.96)**	**4.88 (2.91-8.18)**	**4.54 (2.63-7.84)**
	Home healthcare after discharge		**1.48 (1.03-2.12)**	1.14 (0.77-1.70)	**1.53 (1.06-2.21)**	1.20 (0.80-1.80)
	Any medical technology		**2.60 (1.78-3.80)**	**2.64 (1.78-3.92)**	–	–
Change in Medical Complexity	Any new complex chronic condition		–	–	**1.75 (1.11-2.75)**	1.54 (0.95-2.52)
	Technology assistance	None	–	–	REF	REF
		Preexisting technology	–	–	**3.00 (1.87-4.82)**	**3.46 (2.11-5.68)**
		New technology during admission in children with or without preexisting technology	–	–	**1.84 (1.09-3.10)**	1.60 (0.92-2.80)

[a]Adjusted for patient demographics include age, race/ethnicity, sex, and insurance. Bolded values represent $P < .05$.

(polypharmacy and home healthcare need) remained largely unchanged when adding the change in medical complexity variables (ie, comparing Model 1 and Model 3). However, when accounting for LOS (Model 4), neither the acquisition of a new CCC nor the addition of new technology was associated with readmission. The most common form of new technology was central line followed by nonsurgically placed enteral tube (Appendix Table 2). Finally, in sensitivity analyses (results not detailed), separating new CCC acquired at birth and new CCCs in nonbirth hospitalizations, compared to hospitalizations with no new CCC, yielded similar results as the primary analyses.

DISCUSSION

Higher numbers of scheduled medications prescribed at discharge pose a progressively greater readmission risk for children. The presence of medical technology at admission is associated with subsequent readmission; however, added technology and home healthcare needs were not, when adjusting for patient characteristics and LOS. Additionally, the acquisition of a new CCC was not associated with readmission, when accounting for LOS.

We examined multiple attributes of polypharmacy—the number of scheduled medications, number of as-needed medications, and number of scheduled doses per 24 hours. Interestingly, only the scheduled medications (count of medication and number of doses) were associated with elevated readmission risk. As-needed medications have heterogeneity in the level of importance from critical (eg, seizure rescue) to discretionary (eg, antipyretics, creams). The burden of managing these types of medications may still be high (ie, parents must decide when to administer a critical medication); however, this burden does not translate into increased readmission risk in this population.

Not surprisingly, greater medical complexity—as defined by higher numbers of scheduled discharge medications and technology assistance—is associated with 30-day readmission risk. Our analyses do not allow us to determine how much of the increased risk is due to additional care burden and risks of polypharmacy versus the inherent increase in complexity and severity of illness for which polypharmacy is a marker. Tailoring discharge regimens to the realities of daily life, with the goal of "minimally disruptive medicine"[22,23] (eg, integrating manageable discharge medication routines into school and work schedules), is not a common feature of pediatric discharge planning. For adult patients with complex medical conditions, tailoring medication regimens in a minimally disruptive way is known to improve outcomes.[24] Similarly, adopting minimally disruptive techniques to integrate the polypharmacy inherent in discharge could potentially mitigate some of the readmission risks for children and adolescents.

Contrary to our hypothesis, new technologies and new diagnoses did not confer additional readmission risk when accounting for LOS and patient characteristics. One potential explanation is varying risks conveyed by different types of new

technologies placed during hospitalization. Central lines, the most common form of new technology, is associated with higher odds of reutilization in unadjusted analyses. However, the second most common form of new technology, nonsurgically placed enteral feeding tube, was not. Further analyses of the differential effects of new technology should be further examined in larger datasets. Additionally, the lack of additional readmission risk from new technology may relate to additional teaching and support provided to families of patients undergoing unfamiliar procedures offsets the risks inherent of greater complexity. If so, it may be that the more intensive teaching and postdischarge support provided to families with new technology or a new diagnosis could be replicated through refresher teaching during hospitalizations, when a patient's state of health is status quo for the family (ie, the child was admitted and discharged with the same technology and diagnoses). This notion is supported by prior work that demonstrated successful readmission reduction interventions for children with chronic conditions often rely on enhanced education or coaching.[25,26]

We elected to present models both with and without LOS as a confounder because it is a potentially modifiable attribute of hospitalization. Change in medical complexity aspects were significantly associated with readmission in multivariable models without LOS. However, with the addition of LOS, they were no longer significant. Thus, the readmission risk of new complexity is accounted for by the readmission risk inherent in a longer LOS. This finding prompts additional questions that merit further study: is it that LOS is a general marker for heightened complexity, or is it that a longer LOS can modify readmission risk through additional in-hospital care and time for enhanced education?

Our study has several strengths. We were able to discern true complexity at the time of discharge through medical record review. For example, if a child had a peripherally inserted central catheter placed during hospitalization, it cannot be ascertained through administrative data without medical record review if the technology was removed or in place at discharge. Likewise, medical record review allows for identification of medical technology which is not surgically implanted (eg, nasogastric feeding tubes). Given the "fog" families report as part of their in-hospital experience and its threats to education and postdischarge contingency planning,[17] we felt it important to evaluate medical technology regardless of whether or not it was surgically placed. Additionally, the more detailed and nuanced understanding gained of polypharmacy burden can better inform both risk prediction models and interventions to improve the transition from hospital to home.

This study should also be considered in the context of several limitations. First, the data was from a single children's hospital, so the generalizability of our findings is uncertain. Second, we utilized a novel method for counting new CCCs which compared information collected for clinical purposes (eg, obtaining a past medical history) with data collected for billing purposes (ie, discharge diagnoses). This comparison of information collected for different purposes potentially introduced uncertainty in the classification of diagnoses as new or not new; however, the interrater reliability for adjudicating new diagnoses suggests that the process was reasonably reliable. Third, we did not have access to other hospitals where readmissions could have occurred. While this is a common limitation for readmission studies,[10,12,14,15,18,27-29] we attempted to mitigate any differential risk of being readmitted to other institutions by matching on distance and direction from the hospital. Of note, it is possible that children with medical complexity may be more willing to travel further to the hospital of their choice; thus our matching may be imperfect. However, there is no established method available to identify preadmission medical complexity through administrative data. Finally, the case-control method of the study makes estimating the true incidence of a variety of elements of medical complexity challenging. For example, it is difficult to tell how often children are discharged on five or more medications from a population standpoint when this practice was quite common for cases. Likewise, the true incidence of new technologies and new CCCs is challenging to estimate.

CONCLUSION

Medical complexity at discharge is associated with pediatric readmission risk. Contrary to our hypothesis, the addition of new technologies and new CCC diagnoses are not associated with pediatric readmission, after accounting for patient and hospitalization factors including LOS. The dynamics of LOS as a risk factor for readmission for children with medical complexity are likely multifaceted and merit further investigation in a multi-institutional study.

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Emergency Transfers: An Important Predictor of Adverse Outcomes in Hospitalized Children

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In-hospital arrests are uncommon in pediatrics, making it difficult to identify the risk factors for unrecognized deterioration and to determine the effectiveness of rapid response systems. An emergency transfer (ET) is a transfer from an acute care floor to an intensive care unit (ICU) where the patient received intubation, inotropes, or ≥3 fluid boluses in the first hour after arrival or before transfer. Improvement science work has reduced ETs, but ETs have not been validated against important health outcomes. This case–control study aimed to determine the predictive validity of an ET for outcomes in a free-standing children's hospital. Controls were matched in terms of age, hospital unit, and time of year. Patients who experienced an ET had a significantly higher likelihood of in-hospital mortality (22% vs 9%), longer ICU length of stay (4.9 vs 2.2 days), and longer posttransfer length of stay (26.4 vs 14.7 days) compared with controls (P < .03 for each). *Journal of Hospital Medicine* 2019;14:482-485. Published online first June 7, 2019. © 2019 Society of Hospital Medicine

Unrecognized in-hospital deterioration can result in tragic consequences for pediatric patients. The majority of deterioration events have antecedents such as increasingly abnormal vital signs and new concerns from nurses.[1] Recent meta-analyses have shown that rapid response systems (RRSs), which include trigger mechanisms such as a pediatric early warning score (PEWS), are associated with a reduced rate of arrests and in-hospital mortality.[2,3] Cardiopulmonary arrest rates are useful metrics to judge the effectiveness of the system to identify and respond to deteriorating adult patients; however, there are important challenges to their use as an outcome measure in pediatrics. Arrests, which have been relatively uncommon in pediatric patients, are now even less frequent since the adoption of a RRS in the majority of children's hospitals.[4,5] Several innovations in these systems will be context-dependent and hence best first evaluated in a single center, where arrests outside of the intensive care unit (ICU) may occur rarely. Identification of valid, more frequent proximal measures to arrests may better identify the risk factors for deterioration. This could potentially inform quality improvement efforts to mitigate clinical deterioration.

Bonafide et al. at the Children's Hospital of Philadelphia developed and validated the critical deterioration event (CDE) metric, demonstrating that children who were transferred to the ICU and who received noninvasive ventilation, intubation, or vasopressor initiation within 12 hours of transfer had a >13-fold increased risk of in-hospital mortality.[6] At Cincinnati Children's Hospital Medical Center, an additional proximal outcome measure was developed for unrecognized clinical deterioration, now termed emergency transfers (ETs).[7-9] An ET is defined as any patient transferred to the ICU where the patient received intubation, inotropes, or three or more fluid boluses in the first hour after arrival or before transfer.[9] Improvement science work that aimed at increasing clinician situation awareness was associated with a reduction in ETs,[8] but the association of ETs with mortality or other healthcare utilization outcomes is unknown. The objective of this study was to determine the predictive validity of an ET on in-hospital mortality, ICU length of stay (LOS), and overall hospital LOS.

METHODS

We conducted a case–control study at Cincinnati Children's Hospital, a free-standing tertiary care children's hospital. Our center has had an ICU-based RRS in place since 2005. In 2009, we eliminated the ICU consult such that each floor-to-ICU transfer is evaluated by the RRS. Nurses calculate a Monaghan PEWS every four hours on the majority of nursing units.

Patients of all ages cared for outside of the ICU at any point in their hospitalization from January 1, 2013, to July 31, 2017, were eligible for inclusion. There were no other exclusion criteria. The ICU included both the pediatric ICU and the cardiac ICU.

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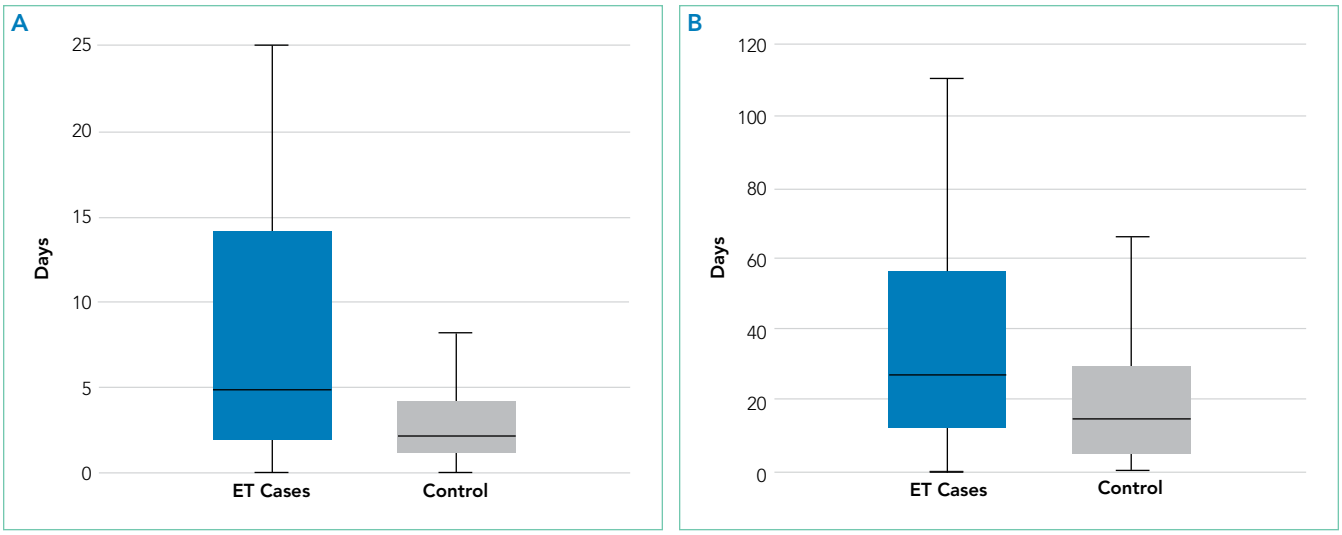

FIG. (A) **ICU length of stay**. ET cases had a median posttransfer ICU length of stay of 4.9 days. Controls had a median posttransfer ICU length of stay of 2.2 days (P = .001). (B) **Hospital length of stay**. ET cases had a median posttransfer hospital length of stay of 26.4 days versus controls with 14.7 days (P = .001).

Abbreviations: ET, emergency transfer; ICU, intensive care unit.

Cases

We identified all ET cases from an existing situation awareness database in which each RRS call is entered by the hospital nursing supervisor, whose role includes responding to each RRS activation. If the patient transfer meets the ET criteria, the nurse indicates this in the database. Each ET entry is later confirmed for assurance purposes by the nurse leader of the RRS committee (RG). For the purposes of this study, all records were again reviewed and validated using manual chart review in the electronic health record (Epic Systems, Verona, Wisconsin).

Controls

We identified nonemergent ICU transfers to serve as controls and matched those to ET in cases to limit the impact of confounders that may increase the likelihood of both an ET and a negative outcome such as ICU mortality. We identified up to three controls for each case from our database and matched in terms of age group (within five years of age), hospital unit before transfer, and time of year (within three months of ET). These variables were chosen to adjust for the impact of age, diversity of disease (as hospital units are generally organized by organ system of illness), and seasonality on outcomes.

Outcome Measures

Posttransfer LOS in the ICU, posttransfer hospital LOS, and in-hospital mortality were the primary outcome measures. Patient demographics, specific diagnoses, and number of medical conditions were a priori defined as covariates of interest. Data for each case and control were entered into a secure, web-based Research Electronic Data Capture (REDCap) database.

Analysis

Descriptive data were summarized using counts and percentages for categorical variables and medians and ranges for continuous variables due to nonnormal distributions. Chi-square test was used to compare in-hospital mortality between the ETs and the controls. The Wilcoxon rank-sum test was used to compare LOS between ETs and controls. All data analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 45 ETs were identified, and 110 controls were matched. Patient demographics were similar among all cases and controls (P > .05). Patients with ETs had a median age of seven years (interquartile range: 3-18 years), and 51% of them were males. The majority of patients among our examined cases were white (68%) and non-Hispanic (93%). There was no statistical difference in insurance between the ETs and the controls. When evaluating the hospital unit before the transfer, ETs occurred most commonly in the Cardiology (22%), Hematology/Oncology (22%), and Neuroscience (16%) units.

ETs stayed longer in the ICU than non-ETs [median of 4.9 days vs 2.2 days, P = .001; Figure (A)]. Similarly, ET cases had a significantly longer posttransfer hospital LOS [median of 35 days vs 21 days, P = .001; Figure (B)]. ETs had a 22% in-hospital mortality rate, compared with 9% in-hospital mortality in the matched controls (P = .02; Table).

DISCUSSION

Children who experienced an ET had a significantly longer ICU LOS, a longer posttransfer LOS, and a higher in-hospital mortality than the matched controls who were also transferred to the ICU. Researchers and improvement science teams at multiple hospitals have demonstrated that interventions targeting improved situation awareness can reduce ETs; we have demonstrated that reducing ETs may reduce subsequent adverse outcomes.[8,10]

These findings provide additional support for the use of the ET metric in children's hospitals as a proximal measure for

TABLE. **In-Hospital Mortality**

	Died n (%)	Survived n (%)	Total
Emergency transfer	10 (22%)	35 (78%)	45
Control	10 (9%)	100 (91%)	110
Total	20	135	155

P = .02

significant clinical deterioration. We found mortality rates that were overall high for a children's hospital (22% in ET cases and 9% among controls) compared with a national average mortality rate of 2.3% in pediatric ICUs.[11] This is likely due to the study sample containing a significant proportion of children with medical complexity.

Aoki et al. recently demonstrated that ETs, compared with non-ETs, were associated with longer LOS and higher mortality in a bivariate analysis.[12] In our study, we found similar results with the important addition that these findings were robust when ETs were compared with matched controls who were likely at a higher risk of poor outcomes than ICU transfers in general. In addition, we demonstrated that ETs were associated with adverse outcomes in a United States children's hospital with a mature, long-standing RRS process. As ETs are considerably more common than cardiac and respiratory arrests, use of the ET metric in children's hospitals may enable more rapid learning and systems improvement implementations. We also found that most of the children with ETs present from units that care for children with substantial medical complexity, including Cardiology, Hematology/Oncology, and Neurosciences. Future work should continue to examine the relationship between medical complexity and ET risk.

The ET metric is complementary to the CDE measure developed by Bonafide et al. Both metrics capture potential events of unrecognized clinical deterioration, and both offer researchers the opportunity to better understand and improve their RRSs. Both ETs and CDEs are more common than arrests, and CDEs are more common than ETs. ETs, which by definition occur in the first hour of ICU care, are likely a more specific measure of unrecognized clinical deterioration. CDEs will capture therapies that may have been started up to 12 hours after transfer and thus are possibly more sensitive to identify unrecognized clinical deterioration. However, CDEs also may encompass some patients who arrived at the ICU after prompt recognition and then had a subacute deterioration in the ICU.

The maturity of the RRS and the bandwidth of teams to collect data may inform which metric(s) are best for individual centers. As ETs are less common and likely more specific to unrecognized clinical deterioration, they might be the first tracked as a center improves its RRS through QI methods. Alternatively, CDEs may be a useful metric for centers where unrecognized clinical deterioration is less common or in research studies where this more common outcome would lead to more power to detect the effect of interventions to improve care.

Our study had several limitations. Data collection was confined to one tertiary care children's hospital with a high burden of complex cardiac and oncology care. The results may not generalize well to children hospitalized in smaller or community hospitals or in hospitals without a mature RRS. There is also the possibility of misclassification of covariates and outcomes, but any misclassification would likely be nondifferential and bias toward the null. Matching was not possible based on exact diagnosis, and the unit is a good but imperfect proxy for diagnosis grouping. At our center, overflow of patients into the Cardiology and Hematology/Oncology units is uncommon, mitigating this partially, although residual confounding may remain. The finding that ETs are associated with adverse outcomes does not necessarily mean that these events were preventable; however, it is important and encouraging that the rate of ETs has been reduced at two centers using improvement science interventions.[8,10]

CONCLUSION

Patients who experienced an ET had a significantly higher likelihood of in-hospital mortality, spent more time in the ICU, and had a longer hospital LOS posttransfer than matched controls. The use of the ET metric in children's hospitals would allow for further analysis of such patients in hopes of identifying clinical characteristics that serve as predictors of deterioration. This may facilitate better risk stratification in the clinical system as well as enable more rapid learning and systems improvements targeted toward preventing unrecognized clinical deterioration.

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Interhospital Transfer: Transfer Processes and Patient Outcomes

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Though often undertaken to provide patients with specialized care, interhospital transfer (IHT) is associated with worse outcomes for select patients. Certain aspects of the transfer process have been suggested as contributors to these outcomes. We performed a retrospective cohort study including patients ≥ 18 years who underwent IHT to a tertiary care hospital between January 2005 and September 2013. We examined the association between "weekend" transfer, "nighttime" transfer, "time delay" between transfer acceptance and arrival, and admission team "busyness" on the day of transfer, and patient outcomes, including transfer to the intensive care unit (ICU) within 48 hours and 30-day mortality. We utilized multivariable logistic regression models, adjusting for patient characteristics. Secondary analyses examined detailed timing of transfer and evaluated 30-day mortality stratified by service of transfer. Among the 24,352 patients who underwent IHT, the nighttime transfer was associated with increased adjusted odds of ICU transfer (odds ratio [OR] 1.54; 95% CI 1.38, 1.72) and 30-day mortality (OR 1.16; 95% CI 1.01, 1.35). Secondary analyses confirmed the association between nighttime transfer and ICU transfer throughout the week and demonstrated that Sunday (and trend towards Friday) night transfers had increased 30-day mortality, as compared with Monday daytime transfer. Stratified analyses demonstrated a significant association between transfer characteristics and adjusted odds of 30-day mortality among cardiothoracic and gastrointestinal surgical service transfers. Our findings suggest high acuity patients have worse outcomes during off-peak times of transfer and during times of high care team workload. Further study is needed to identify underlying reasons to explain these associations and devise potential solutions. *Journal of Hospital Medicine* 2019;14:486-491. Published April 8, 2019. © 2019 Society of Hospital Medicine

The transfer of patients between acute care hospitals (interhospital transfer [IHT]) occurs regularly among patients with a variety of diagnoses, in theory, to gain access to unique specialty services and/or a higher level of care, among other reasons.[1,2]

However, the practice of IHT is variable and nonstandardized,[3,4] and existing data largely suggests that transferred patients experience worse outcomes, including longer length of stay, higher hospitalization costs, longer ICU time, and greater mortality, even with rigorous adjustment for confounding by indication.[5,6] Though there are many possible reasons for these findings, existing literature suggests that there may be aspects of the transfer process itself which contribute to these outcomes.[2,6,7]

Understanding which aspects of the transfer process contribute to poor patient outcomes is a key first step toward the development of targeted quality improvement initiatives to improve this process of care. In this study, we aim to examine the association between select characteristics of the transfer process, including the timing of transfer and workload of the admitting physician team, and clinical outcomes among patients undergoing IHT.

METHODS

Data and Study Population

We performed a retrospective analysis of patients ≥age 18 years who transferred to Brigham and Women's Hospital (BWH), a 777-bed tertiary care hospital, from another acute care hospital between January 2005, and September 2013. Dates of inclusion were purposefully chosen prior to BWH implementation of a new electronic health records system to avoid potential information bias. As at most academic medical centers, night coverage at BWH differs by service and includes a combination of long-call admitting teams and night float coverage. On weekends, many services are less well staffed, and some procedures may only be available if needed emergently. Some services have caps on the daily number of admissions or total patient census, but none have caps on the number of discharges per day. Patients were excluded from analysis if they left BWH against medical advice, were transferred from closely affiliated hospitals with shared personnel and electronic health records (Brigham and Women's Faulkner Hospital, Dana Farber Cancer Institute), transferred from inpatient psychiatric or inpatient hospice facilities, or transferred to obstetrics or nursery services. Data were obtained from administrative sources and the research patient data repository (RPDR), a centralized clinical data repository that gathers data from various hospital legacy systems and stores them in one data warehouse.[8] Our

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study was approved by the Partners Institutional Review Board (IRB) with a waiver of patient consent.

Transfer Process Characteristics

Predictors included select characteristics of the transfer process, including (1) Day of week of transfer, dichotomized into Friday through Sunday ("weekend"), versus Monday through Thursday ("weekday");[9] Friday was included with "weekend" given the suggestion of increased volume of transfers in advance of the weekend; (2) Time of arrival of the transferred patient, categorized into "daytime" (7 AM-5 PM), "evening" (5 PM -10 PM), and "nighttime" (10 PM -7 AM), with daytime as the reference group; (3) Admitting team "busyness" on day of patient transfer, defined as the total number of additional patient admissions and patient discharges performed by the admitting team on the calendar day of patient arrival, as has been used in prior research,[10] and categorized into quartiles with lowest quartile as the reference group. Service-specific quartiles were calculated and used for stratified analyses (described below); and (4) "Time delay" between patient acceptance for transfer and patient arrival at BWH, categorized into 0-12 hours, 12-24 hours, 24-48 hours, and >48 hours, with 12-24 hours as the reference group (anticipating that time delay of 0-12 hours would be reflective of "sicker" patients in need of expedited transfer).

Outcomes

Outcomes included transfer to the intensive care unit (ICU) within 48 hours of arrival and 30-day mortality from date of index admission.[5,6]

Patient Characteristics

Covariates for adjustment included: patient age, sex, race, Elixhauser comorbidity score,[11] Diagnosis-Related Group (DRG)-weight, insurance status, year of admission, number of preadmission medications, and service of admission.

Statistical Analyses

We used descriptive statistics to display baseline characteristics and performed a series of univariable and multivariable logistic regression models to obtain the adjusted odds of each transfer process characteristic on each outcome, adjusting for all covariates (proc logistic, SAS Statistical Software, Cary, North Carolina). For analyses of ICU transfer within 48 hours of arrival, all patients initially admitted to the ICU at time of transfer were excluded.

In the secondary analyses, we used a combined day-of-week and time-of-day variable (ie, Monday day, Monday evening, Monday night, Tuesday day, and so on, with Monday day as the reference group) to obtain a more detailed evaluation of timing of transfer on patient outcomes. We also performed stratified analyses to evaluate each transfer process characteristic on adjusted odds of 30-day mortality stratified by service of admission (ie, at the time of transfer to BWH), adjusting for all covariates. For all analyses, two-sided *P* values < .05 were considered significant.

TABLE 1. **Baseline Characteristics of Transferred Patients**

Characteristic	Transferred Patients (N = 24,352)
Patient Characteristics	
Age in years, mean (SD)[a]	62.2 (16.3)
Male sex, n (%)	13,647 (56.0)
Race, n (%)	
White	20,466 (84.0)
Black	759 (3.1)
Hispanic	255 (1.0)
Other	2,872 (11.8)
Insurance, n (%)	
Medicare	13,231 (54.3)
Medicaid	1,532 (6.3)
Private	8,958 (36.8)
Other	631 (2.6)
Admit year, n (%)	
2005	2,715 (11.2)
2006	2,768 (11.4)
2007	2,817 (11.6)
2008	2,777 (11.4)
2009	2,849 (11.7)
2010	2,805 (11.5)
2011	2,789 (11.5)
2012	2,730 (11.2)
2013	2,102 (8.6)
Admission service, n (%)	
Cardiology	9,190 (37.7)
CT Surgery	3,156 (13.0)
Medicine[b]	2,466 (10.1)
Oncology/BMT	2,183 (9.0)
Neurology	1,456 (6.0)
ICU[c]	1,442 (5.9)
Orthopedic/Burn/Trauma	1,235 (5.1)
GI Surgery	1,066 (4.4)
Neurosurgery	768 (3.2)
Other[d]	912 (3.7)
Elixhauser comorbidity score, mean (SD)[a]	7.2 (7.8)
DRG-weight, mean (SD)[a]	2.8 (2.9)
Number of preadmission medications quartile, n (%)	
0-1	5,225 (21.5)
2-6	5,777 (23.7)
7-10	4,549 (18.7)
≥11	4,677 (19.2)
Missing patient data	4,124 (16.9)
Transfer Process Characteristics	
Weekday transfer (Monday-Thursday), n (%)	14,612 (60.0)
Time of day of transfer, n (%)	
Daytime (7 AM - 5 PM)	7,917 (32.5)
Evening (5 PM - 10 PM)	12,597 (51.7)
Nighttime (10 PM - 7 AM)	3,838 (15.8)
Admission team busyness[e] on day of patient transfer-quartiles, n (%)	
0-4	5,393 (22.2)
5-7	7,382 (30.3)
8-10	6,012 (24.7)
≥10	5,565 (22.8)
Time delay between transfer acceptance and patient arrival (hours), n (%)	
0-12 hours	17,896 (74.3)
>12-24 hours	1,766 (7.3)
>24-48 hours	3,080 (12.8)
>48 hours	1,336 (5.5)

[a]Categorized into quartiles for multivariable regression analyses
[b]Medicine service includes: General medicine, gastroenterology, renal, endocrine, hypertension, infectious disease, and rheumatology services.
[c]ICU patients were excluded in all regression analyses examining odds of ICU transfer within 48 hours of admission
[d]Other service includes: otolaryngology, urology, plastic surgery, gynecology, dental, and other services
[e]Busyness defined as total number of other patient admissions and discharges by admission team on day of patient transfer
Abbreviations: BMT, bone marrow transplant; CT, cardiothoracic; DRG, diagnosis-related group; GI, gastrointestinal; ICU, intensive care unit; SD, standard deviation.

TABLE 2. **Association of Transfer Process Characteristics and Adjusted Odds of ICU Transfer and 30-Day Mortality**

Transfer Process Characteristic	ICU Transfer within 48 hours, n (%)[a]	Unadjusted OR (95% CI)[b]	Adjusted OR (95% CI)
Day of Week of Arrival			
Weekend, n = 9,088	2,020 (22%)	*0.83 (0.77, 0.88)*	0.93 (0.87,1.01)
Weekday, n = 13,774	3,598 (26%)	Ref	Ref
Time of Day of Arrival			
Nighttime, n = 3,449	1,233 (36%)	*1.57 (1.43, 1.72)*	*1.54 (1.38, 1.72)*
Daytime, n = 7,521	1,813 (24%)	Ref	Ref
Admitting team busyness			
≥10, n = 5,180	854 (16%)	*0.40 (0.37, 0.44)*	*0.53 (0.48, 0.59)*
0-4, n = 7,399	2,448 (33%)	Ref	Ref
Time Delay between Acceptance/Arrival			
>48 hours	172 (13.2%)	1.00 (0.81, 1.24)	0.86 (0.67, 1.08)
12-24 hours	239 (14%)	Ref	Ref
Transfer Process Characteristic	**30-Day Mortality, n (%)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)[a]**
Day of Week of Arrival			
Weekend, n = 9,726	953 (9.8%)	*1.14 (1.05,1.25)*	1.06 (0.96,1.18)
Weekday, n = 14,588	1,262 (8.7%)	Ref	Ref
Time of Day of Arrival			
Nighttime, n = 3,828	449 (12%)	*1.67 (1.46,1.90)*	*1.16 (1.01, 1.35)*
Daytime, n = 7,894	565 (7.2%)	Ref	Ref
Admitting team busyness			
≥10, n = 5,414	389 (7.2%)	*0.77 (0.67,0.87)*	0.89 (0.77, 1.02)
0-4, n = 7,966	749 (9.4%)	Ref	Ref
Time Delay between Acceptance/Arrival			
>48 hours	108 (8.1%)	0.97 (0.74, 1.26)	0.88 (0.66,1.17)
12-24 hours	135 (7.6%)	Ref	Ref

[a]Excluded ICU service patients
[b]Adjusted for all patient characteristics (Table), and all other transfer process characteristics
Abbreviations: CI, confidence interval; ICU, intensive care unit; OR, odds ratio; Ref, referent.
Definitions: Weekday, Monday through Thursday; Weekend, Friday through Sunday; Nighttime, 10 PM - 7 AM, Daytime = 7 AM - 5 PM; Admitting team busyness, Number of additional patient admissions + discharges performed by admitting team on day of patient arrival.

RESULTS

Overall, 24,352 patients met our inclusion criteria and underwent IHT, of whom 2,174 (8.9%) died within 30 days. Of the 22,910 transferred patients originally admitted to a non-ICU service, 5,464 (23.8%) underwent ICU transfer within 48 hours of arrival. Cohort characteristics are shown in Table 1.

Multivariable regression analyses demonstrated no significant association between weekend (versus weekday) transfer or increased time delay between patient acceptance and arrival (>48 hours) and adjusted odds of ICU transfer within 48 hours or 30-day mortality. However, they did demonstrate that nighttime (versus daytime) transfer was associated with greater adjusted odds of both ICU transfer and 30-day mortality. Increased admitting team busyness was associated with *lower* adjusted odds of ICU transfer but was not significantly associated with adjusted odds of 30-day mortality (Table 2). As expected, *decreased* time delay between patient acceptance and arrival (0-12 hours) was associated with increased adjusted odds of both ICU transfer (adjusted OR 2.68; 95% CI 2.29, 3.15) and 30-day mortality (adjusted OR 1.25; 95% CI 1.03, 1.53) compared with 12-24 hours (results not shown). Time delay >48 hours was not associated with either outcome.

Regression analyses with the combined day/time variable demonstrated that compared with Monday daytime transfer, Sunday night transfer was significantly associated with increased adjusted odds of 30-day mortality, and Friday night transfer was associated with a trend toward increased 30-day mortality (adjusted OR [aOR] 1.88; 95% CI 1.25, 2.82, and aOR 1.43; 95% CI 0.99, 2.06, respectively). We also found that all nighttime transfers (ie, Monday through Sunday night) were associated with increased adjusted odds of ICU transfer within 48 hours (as compared with Monday daytime transfer). Other days/time analyses were not significant.

Univariable and multivariable analyses stratified by service were performed (Appendix). Multivariable stratified analyses demonstrated that weekend transfer, nighttime transfer, and increased admitting team busyness were associated with increased adjusted odds of 30-day mortality among cardiothoracic (CT) and gastrointestinal (GI) surgical service patients. Increased admitting team busyness was also associated with increased mortality among ICU service patients but was associated with *decreased* mortality among cardiology service patients. An increased time delay between patient acceptance and arrival was associated with *decreased* mortality among CT and GI surgical service patients (Figure; Appendix). Other adjusted stratified outcomes were not significant.

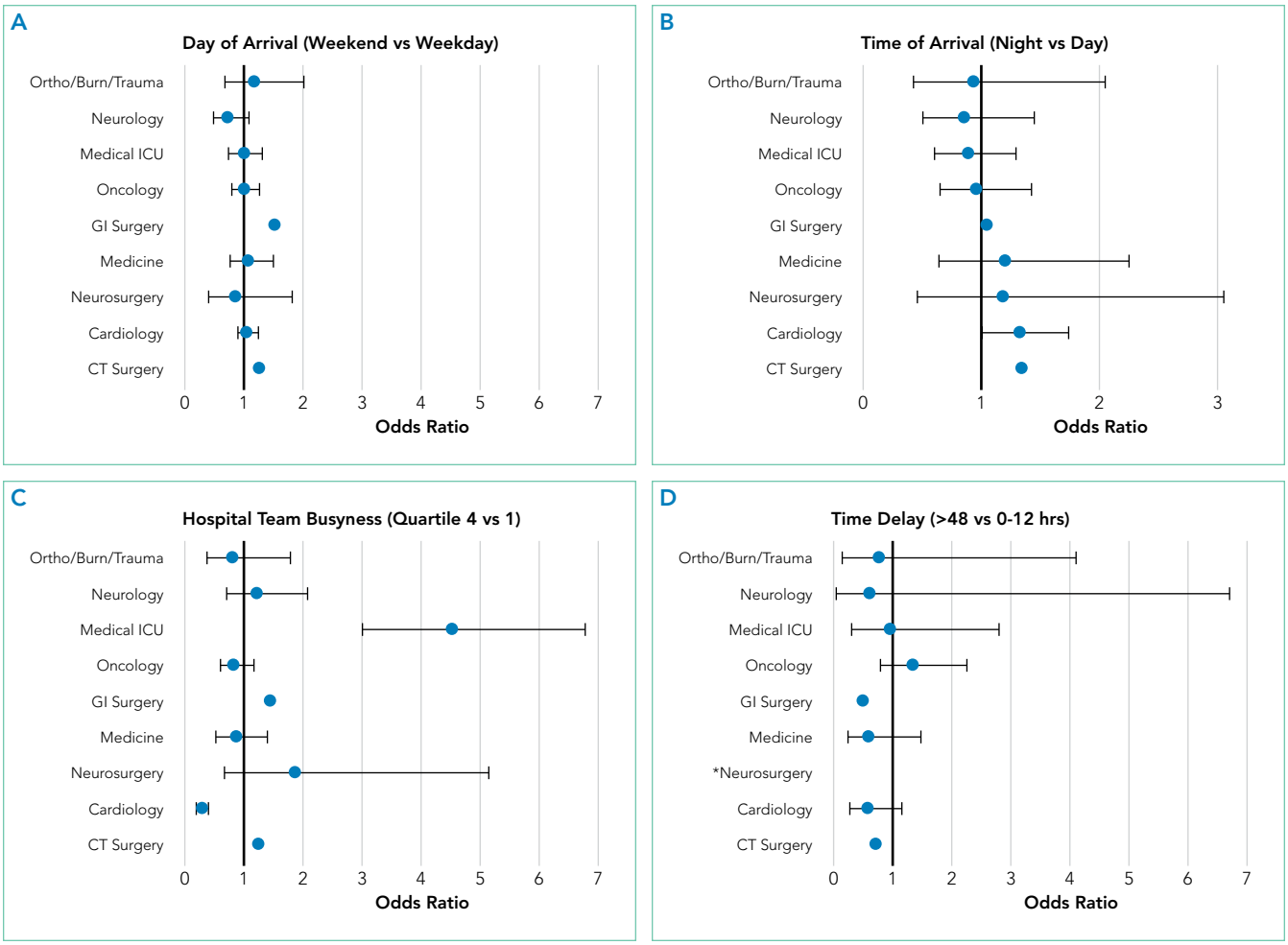

FIG. Association of Transfer Process Characteristic with Adjusted Odds of 30-day Mortality Stratified by Service.

*Too few outcomes to perform stratified analyses for association of increased time delay and adjusted odds of 30-day mortality among neurosurgical service transfers
Service-specific quartiles were calculated and used for Hospital Team busyness analysis (Appendix)

Abbreviations: CT, Cardiothoracic; GI, Gastrointestinal; ICU, Intensive Care Unit; Ortho, Orthopedics

DISCUSSION

In this study of 24,352 patients undergoing IHT, we found no significant association between weekend transfer or increased time delay between transfer acceptance and arrival and patient outcomes in the cohort as a whole; but we found that nighttime transfer is associated with increased adjusted odds of both ICU transfer within 48 hours and 30-day mortality. Our analyses combining day-of-week and time-of-day demonstrate that Sunday night transfer is particularly associated with increased adjusted odds of 30-day mortality (as compared with Monday daytime transfer), and show a trend toward increased mortality with Friday night transfers. These detailed analyses otherwise reinforce that nighttime transfer across all nights of the week is associated with increased adjusted odds of ICU transfer within 48 hours. We also found that increased admitting team busyness on the day of patient transfer is associated with *decreased* odds of ICU transfer, though this may solely be reflective of higher turnover services (ie, cardiology) caring for lower acuity patients, as suggested by secondary analyses stratified by service. In addition, secondary analyses demonstrated differential associations between weekend transfers, nighttime transfers, and increased team busyness on the odds of 30-day mortality based on service of transfer. These analyses showed that patients transferred to higher acuity services requiring procedural care, including CT surgery, GI surgery, and Medical ICU, do worse under all three circumstances as compared with patients transferred to other services. Secondary analyses also demonstrated that increased time delay between patient acceptance and arrival is inversely associated with 30-day mortality among CT and GI surgery service patients, likely reflecting lower acuity patients (ie, less sick patients are less rapidly transferred).

There are several possible explanations for these findings. Patients transferred to surgical services at night may reflect a more urgent need for surgery and include a sicker cohort of patients, possibly explaining these findings. Alternatively, or in addition, both weekend and nighttime hospital admission expose patients to similar potential risks, ie, limited resources available during off-peak hours. Our findings could, therefore, reflect the possibility that patients transferred to higher acui-

ty services in need of procedural care are most vulnerable to off-peak timing of transfer. Similar data looking at patients admitted through the emergency room (ER) find the strongest effect of off-peak admissions on patients in need of procedures, including GI hemorrhage,[12] atrial fibrillation[13] and acute myocardial infarction (AMI),[14] arguably because of the limited availability of necessary interventions. Patients undergoing IHT are a sicker cohort of patients than those admitted through the ER, and, therefore, may be even more vulnerable to these issues.[3,5] This is supported by our findings that Sunday night transfers (and trend toward Friday night transfers) are associated with greater mortality compared with Monday daytime transfers, when at-the-ready resources and/or specialty personnel may be less available (Sunday night), and delays until receipt of necessary procedures may be longer (Friday night). Though we did not observe similar results among cardiology service transfers, as may be expected based on existing literature,[13,14] this subset of patients includes more heterogeneous diagnoses, (ie, not solely those that require acute intervention) and exhibited a low level of acuity (low Elixhauser score and DRG-weight, data not shown).

We also found that increased admitting team busyness on the day of patient transfer is associated with increased odds of 30-day mortality among CT surgery, GI surgery, and ICU service transfers. As above, there are several possible explanations for this finding. It is possible that among these services, only the sickest/neediest patients are accepted for transfer when teams are busiest, explaining our findings. Though this explanation is possible, the measure of team "busyness" includes patient discharge, thereby increasing, not decreasing, availability for incoming patients, making this explanation less likely. Alternatively, it is possible that this finding is reflective of reverse causation, ie, that teams have less ability to discharge/admit new patients when caring for particularly sick/unstable patient transfers, though this assumes that transferred patients arrive earlier in the day, (eg, in time to influence discharge decisions), which infrequently occurs (Table 1). Lastly, it is possible that this subset of patients will be more vulnerable to the workload of the team that is caring for them at the time of their arrival. With high patient turnover (admissions/discharges), the time allocated to each patient's care may be diminished (ie, "work compression," trying to do the same amount of work in less time), and may result in decreased time to care for the transferred patient. This has been shown to influence patient outcomes at the time of patient discharge.[10]

In trying to understand why we observed an inverse relationship between admitting team busyness and odds of ICU transfer within 48 hours, we believe this finding is largely driven by cardiology service transfers, which comprise the highest volume of transferred patients in our cohort (Table 1), and are low acuity patients. Within this population of patients, admitting team busyness is likely a surrogate variable for high turnover/low acuity. This idea is supported by our findings that admitting team busyness is associated with *decreased* adjusted odds of 30-day mortality in this group (and only in this group).

Similarly, our observed inverse relationship between increased time delay and 30-day mortality among CT and GI surgical service patients is also likely reflective of lower acuity patients. We anticipated that decreased time delay (0-12 hours) would be reflective of greater patient acuity (supported by our findings that *decreased* time delay is associated with *increased* odds of ICU transfer and 30-day mortality). However, our findings also suggest that increased time delay (>48 hours) is similarly representative of lower patient acuity and therefore an imperfect measure of discontinuity and/or harmful delays in care during IHT (see limitations below).

Our study is subject to several limitations. This is a single site study; given known variation in transfer practices between hospitals,[3] it is possible that our findings are not generalizable. However, given similar existing data on patients admitted through the ER, it is likely our findings may be reflective of IHT to similar tertiary referral hospitals. Second, although we adjusted for patient characteristics, there remains the possibility of unmeasured confounding and other bias that account for our results, as discussed. Third, although the definition of "busyness" used in this study was chosen based on prior data demonstrating an effect on patient outcomes,[10] we did not include other measures of busyness that may influence outcomes of transferred patients such as overall team census or hospital busyness. However, the workload associated with a high volume of patient admissions and discharges is arguably a greater reflection of "work compression" for the admitting team compared with overall team census, which may reflect a more static workload with less impact on the care of a newly transferred patient. Also, although hospital census may influence the ability to transfer (ie, lower volume of transferred patients during times of high hospital census), this likely has less of an impact on the direct care of transferred patients than the admitting team's workload. It is more likely that it would serve as a confounder (eg, sicker patients are accepted for transfer despite high hospital census, while lower risk patients are not).

Nevertheless, future studies should further evaluate the association with other measures of busyness/workload and outcomes of transferred patients. Lastly, though we anticipated time delay between transfer acceptance and arrival would be correlated with patient acuity, we hypothesized that longer delay might affect patient continuity and communication and impact patient outcomes. However, our results demonstrate that our measurement of this variable was unsuccessful in unraveling patient acuity from our intended evaluation of these vulnerable aspects of IHT. It is likely that a more detailed evaluation is required to explore potential challenges more fully that may occur with greater time delays (eg, suboptimal communication regarding changes in clinical status during this time period, delays in treatment). Similarly, though our study evaluates the association between nighttime and weekend transfer (and the interaction between these) with patient outcomes, we did not evaluate other intermediate outcomes that may be more affected by the timing of transfer, such as diagnostic errors or delays in procedural care, which warrant further investigation. We do not directly examine the underly-

ing reasons that explain our observed associations, and thus more research is needed to identify these as well as design and evaluate solutions.

Collectively, our findings suggest that high acuity patients in need of procedural care experience worse outcomes during off-peak times of transfer, and during times of high care-team workload. Though further research is needed to identify underlying reasons to explain our findings, both the timing of patient transfer (when modifiable) and workload of the team caring for the patient on arrival may serve as potential targets for interventions to improve the quality and safety of IHT for patients at greatest risk.

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Association of Herpes Simplex Virus Testing with Hospital Length of Stay for Infants ≤60 Days of Age Undergoing Evaluation for Meningitis

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Although neonatal herpes simplex virus (HSV) causes significant morbidity, utilization of the cerebrospinal fluid (CSF) HSV polymerase chain reaction (PCR) test remains variable. Our objective was to examine the association of CSF HSV PCR testing with length of stay (LOS) in a 20-center retrospective cohort of hospitalized infants aged ≤60 days undergoing evaluation for meningitis after adjustment for patient-level factors and clustering by center. Of 20,496 eligible infants, 7,399 (36.1%) had a CSF HSV PCR test performed, and 46 (0.6% of those tested) had a positive test. Infants who had a CSF HSV PCR test performed had a 23% longer hospital LOS (incident rate ratio 1.23; 95% CI: 1.14-1.33). Targeted CSF HSV PCR testing may mitigate the impact on LOS for low-risk infants. *Journal of Hospital Medicine* 2019;14:492-495. Published online first May 10, 2019. © 2019 Society of Hospital Medicine

Neonatal herpes simplex virus (HSV) is associated with significant morbidity and mortality,[1] particularly when the diagnosis or treatment is delayed.[2] Therefore, many infants aged ≤60 days being evaluated for meningitis undergo cerebrospinal fluid (CSF) HSV polymerase chain reaction (PCR) testing even though the risk of HSV infection is low [estimated at 0.4% of those undergoing evaluation for central nervous system (CNS) infection].[3] A single-center study demonstrated that CSF HSV PCR testing increases the hospital length of stay (LOS) for infants aged ≤56 days,[4] although these single-center findings may not be generalizable. To this end, we measured the association between CSF HSV PCR testing and LOS in a multicenter cohort of hospitalized young infants.

METHODS

Study Design

We conducted a planned secondary analysis of a retrospective cohort of infants aged ≤60 days who presented to the emergency department (ED) between January 1, 2005 and December 31, 2013, enrolled in the Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) HSV study.[3] Our study was limited to the 20 hospitals that contributed hospital LOS data. The study protocol was approved by each site's institutional review board with permission for data sharing.

Study Population

Eligible infants were identified at each site using a site-specific electronic search strategy. Infants were eligible for inclusion if a CSF culture was obtained in the ED or within 24 hours of ED arrival. We excluded infants who were discharged from the ED and those with missing hospital LOS data.

Data Collection

Site investigators extracted the following data elements either electronically or from medical records: patient demographics; ED arrival date and time; hospital discharge date and time; urinalysis results; peripheral and CSF cell counts; blood, urine, and CSF bacterial culture results; as well as the results of HSV PCR and viral cultures. Infants with growth of a pathogen in blood or CSF, or a catheterized urine culture with ≥50,000 colony-forming units (CFUs)/mL of a single pathogenic bacteria, or 10,000-50,000 CFUs/mL of a single pathogenic bacteria with

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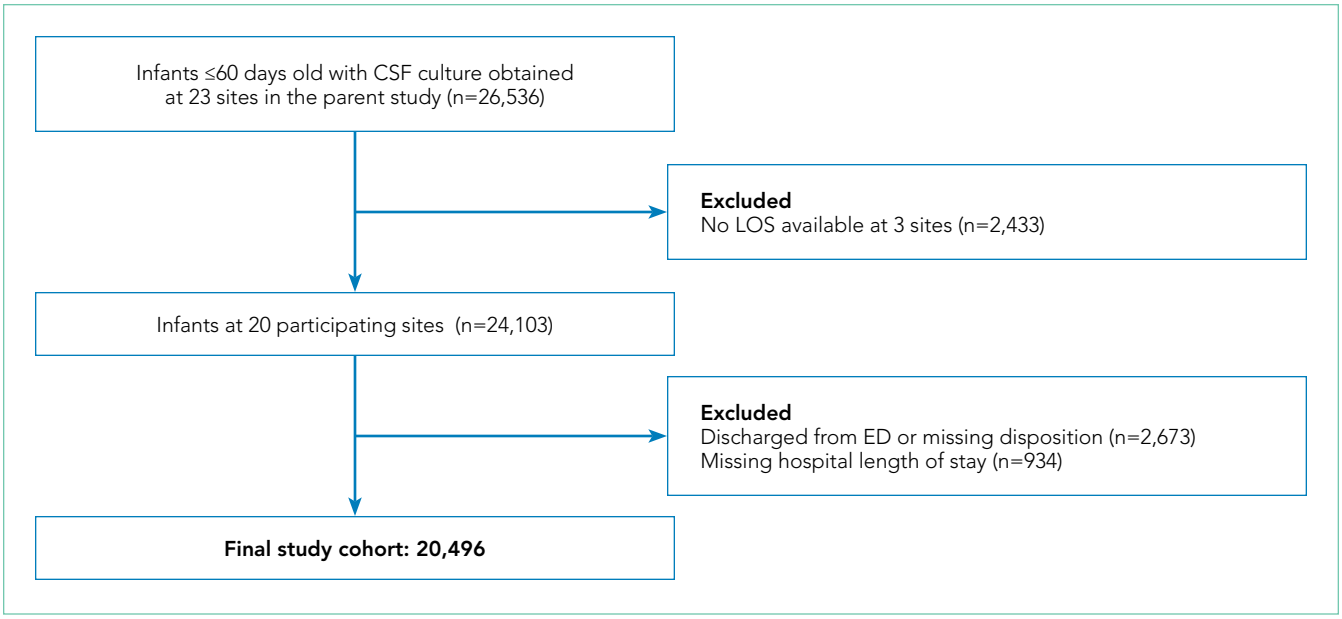

FIG. Study Cohort.

Abbreviations: CSF, cerebrospinal fluid; ED, emergency department; LOS, length of stay.

an abnormal urinalysis (ie, positive nitrite or leukocyte esterase on urine dipstick or >5 white blood cells [WBCs] per high power field on urine microscopy) were classified as having a serious bacterial infection (SBI).[5,6] Infants with a positive HSV PCR or viral culture from any site were classified as having HSV infection.[3] Hospitalized infants who did not have an HSV PCR test performed were assumed not to have HSV disease if not diagnosed during the hospital stay or repeat ED encounter.[3]

Outcome Measures

The primary outcome was hospital LOS, defined at all hospitals as the time from ED arrival to provider signature of the hospital discharge order, calculated in minutes and then converted into days.

Statistical Analysis

We described LOS using medians with interquartile ranges (IQR) and compared between infants with and without a CSF HSV PCR test performed using the Mann–Whitney U test. To evaluate the association between performance of CSF HSV PCR testing and hospital LOS, we used negative binomial regression given the count variable outcome (LOS) with an overdispersed distribution. For this analysis, we clustered by hospital after adjusting for the following factors determined *a priori*: age, gender, study year, and presence of serious bacterial or HSV infection. Using the relative marginal modeled estimates of LOS (tested vs not tested), we determined the percentage increase in LOS. We then repeated the analyses after stratifying by the location of testing (ie, in-house vs send-out), age (≤28 days vs 29-60 days), and presence or absence of CSF pleocytosis (defined as a CSF WBC of ≥16 cells/mm^3 for infants aged ≤28 days and ≥10 cells/mm^3 for infants aged 29-60 days),[7] because infants aged 29-60 days and those without CSF pleocytosis are reported to be at very low risk for CNS HSV infection.[3,8] We utilized Stata Data Analysis and Statistical Software, version 15.0 (StataCorp, Inc.; College Station, Texas) for statistical analyses.

RESULTS

Of 24,103 infants with CSF cultures obtained at the 20 participating sites, we excluded 2,673 (11.1%) discharged from the ED or with missing disposition and 934 (3.9%) with missing LOS, leaving a study cohort of 20,496 infants (Figure). Overall, 1,780 infants (8.7%) had an SBI and 99 (0.5%) had an HSV infection, of which 46 (46.5%) had a CNS HSV infection.

Among the 20,496 study infants, 7,399 (36.1%) had a CSF HSV PCR test performed; 5,935 infants (80.2% of those tested) had in-house and 1,464 (19.8%) had send-out testing. Among infants with available CSF cell counts, a CSF HSV PCR test was more commonly performed in infants with CSF pleocytosis than in those without (1,865/4,439 [42.0%] with CSF pleocytosis vs 3,705/12,002 [30.9%] without CSF pleocytosis; odds ratio [OR] 1.6, 95% CI 1.5-1.7). Of the 7,399 infants who had a CSF HSV PCR test performed, 46 (0.6%) had a positive test. Of the tested infants, 5,570 (75.3%) had an available CSF WBC count; a positive CSF HSV PCR test was more common in infants with CSF pleocytosis than in those without (25 positive tests/1,865 infants with CSF pleocytosis [1.3%] vs 9/3,705 [0.2%] without CSF pleocytosis; OR 5.6, 95% CI 2.6-12.0). Among the 5,308 infants aged 29-60 days without CSF pleocytosis, 1,110 (20.9%) had a CSF HSV PCR test performed and only one infant (0.09% of those tested) had a positive test.

Without adjustment, infants with a CSF HSV PCR test had a longer median LOS than infants who were not tested (2.5 vs 2.3 days; $P < .001$). After adjustment, infants with a CSF HSV PCR test performed had a 23% longer duration of hospitalization. The association between testing and LOS was similar for older

TABLE. **Length of Stay for Hospitalized Infants with a CSF HSV PCR Test Performed versus Infants without a CSF HSV PCR Test Performed**

	N	CSF HSV PCR LOS in Days Median (IQR)[a]	No CSF HSV PCR LOS in Days Median (IQR)[a]	IRR (95% CI)[b]	% Increase in LOS[c]
Overall	20,496	2.5 (2.0-3.8)	2.3 (1.9-3.0)	1.23 (1.14-1.33)	23%
Age					
≤28 days	11,269	2.6 (2.1-3.9)	2.4 (2.0-3.4)	1.19 (1.13-1.27)	19%
29-60 days	9,227	2.4 (2.0-3.5)	2.2 (1.8-2.9)	1.28 (1.12-1.47)	28%
CSF Pleocytosis					
CSF Pleocytosis	4,439	2.6 (2.1-3.9)	2.3 (1.8-2.9)	1.23 (1.15-1.31)	23%
No CSF pleocytosis	12,002	2.6 (2.1-4.0)	2.3 (1.9-3.0)	1.24 (1.15-1.35)	24%
Testing Location					
In house	14,928	2.5 (2.0-3.7)	2.3 (1.9-3.0)	1.22 (1.12-1.33)	22%
Send out	5,568	2.7 (2.1-4.3)	2.3 (1.9-3.1)	1.28 (1.05-1.57)	28%

[a]Unadjusted LOS

[b]Adjusted for age, gender, presence of serious bacterial or HSV infection, and study year, clustered by hospital using robust standard errors

[c]Using relative marginal modeled estimates of LOS (Tested vs Not Tested) from adjusted model

Abbreviations: CSF, cerebrospinal fluid; IQR, interquartile range; IRR, internal rate of return, HSV, herpes simplex virus; LOS, length of stay; PCR, polymerase chain reaction.

vs younger infants, infants with and without CSF pleocytosis, and in-house vs send-out testing (Table).

DISCUSSION

In a large, multicenter cohort of more than 20,000 hospitalized infants aged ≤60 days undergoing evaluation for meningitis, we examined the association of CSF HSV PCR testing with hospital LOS. Approximately one-third of study infants had a CSF HSV PCR test obtained. After adjustment for patient- and hospital-level factors, the treating clinician's decision to obtain a CSF HSV PCR test was associated with a 23% longer hospital LOS (nearly one-half day).

Our findings are consistent with those of previous studies. First, our observed association of the decision to obtain a CSF HSV PCR test and LOS was similar in magnitude to that of a previous single-center investigation.[4] Second, we also found that older infants and those without CSF pleocytosis were at very low risk of HSV infection.[3,8] For the otherwise low-risk infants, the longer LOS may be due to delays in obtaining CSF HSV PCR test results, which should be explored in future research. Our study has greater generalizability than previous single-center studies by substantially increasing the population size as well as the variety of clinical settings. Ensuring clinicians' access to rapid HSV PCR testing platforms will further mitigate the impact of HSV testing on LOS.

When deciding to perform a CSF HSV PCR test for infants aged ≤60 days, clinicians must balance the low incidence of neonatal HSV[3] with the risk of delayed diagnosis and treatment of HSV infection, which include neurologic sequelae or even death.[1,2] As infants with CNS HSV infection commonly present nonspecifically and only a minority of infected infants have skin vesicles,[1] controversy exists as to which infants should be evaluated for HSV infection, resulting in considerable variability in HSV testing.[3] Some clinicians advocate for more conservative testing strategies that include the performance of CSF HSV PCR testing in all febrile infants aged ≤21 days.[9] Others suggest limiting testing to infants who meet high-risk criteria (eg, seizures, ill-appearance, or CSF pleocytosis).[10,11] Further investigation will need to elucidate the clinical and laboratory predictors of HSV infection to identify those infants who would benefit most from HSV testing as well as the outcomes of infants not tested.

Our study has several limitations. First, we could not determine the reason why clinicians elected to obtain a CSF HSV PCR test, and we do not know the test turnaround time or the time when results became available to the clinical team. Second, we did not abstract clinical data such as ill-appearance or seizures. Although we adjusted for the presence of serious bacterial or HSV infection as proxy measures for illness severity, it is possible that other clinical factors were associated with HSV testing and LOS. Third, although we adjusted for patient- and hospital-level factors in our regression model, the potential for residual confounding persists. Fourth, we did not explore acyclovir administration as a factor associated with LOS as some sites did not provide data on acyclovir. Fifth, we did not evaluate the impact of HSV testing of other sample types (eg, blood or skin) on LOS. Sixth, our study was conducted primarily at children's hospitals, and our findings may not be generalizable to general hospitals with hospitalized neonates.

CONCLUSIONS

For infants aged ≤60 days undergoing evaluation for meningitis, CSF HSV PCR testing was associated with a slightly longer hospi-

tal LOS. Improved methods to identify and target testing to higher risk infants may mitigate the impact on LOS for low-risk infants.

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Mission-Driven Criteria for Life and Career

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"I think healthcare is more about love than most other things"
—Don Berwick

Dr. Berwick speaks of the relationship between the doctor and the patient and family. I believe this relationship is sacred. My job as CEO of Blue Cross North Carolina is hard. But it was so much harder on a recent weekend to give a new diagnosis of a certainly fatal disease of a less than 1-year old child to her parents and discuss palliative care options. I cried and they cried. Being a leader, particularly in healthcare, requires us to maintain sight of what is important and return to those things often as we lead.

Growing up, my parents stressed two things: service and education. I decided early on that I wanted to improve our health care system. I have had a sometimes-winding path to this goal - including work as a consultant, medical school and residency, an RWJ Clinical Scholar, clinical work as a pediatric hospitalist and two tours through government as a White House Fellow, the Centers for Medicare and Medicaid Services (CMS) as Chief Medical Officer, Deputy Administrator and leader of the CMS Innovation Center. With each step I have used five criteria that have allowed me to consider decisions while staying true to myself and my mission.

First, Family. My wife and I have four children, age 10 and under. I put them first as I make decisions.

Second, Impact. Better quality, lower costs, and exceptional experience for populations of people. The triple aim, as we better know it.

Third, People. In the beginning, I took jobs to work with specific mentors. Now, I look carefully at the people and culture where I serve to assess fit and how I could uniquely add value.

Fourth, Learning. How much will I learn every day? When I interviewed for my current job, I told them that they could hire an insurance executive who would be better on day one than me, but if they wanted someone who would improve every day and try to make a model of health transformation and a model health plan for the nation, then they should choose me.

Fifth, Joy in Work. Self-explanatory.

We also have a family mission statement, which was my wife's good idea. We wrote it together right after we were married. It is too personal to share in detail, but it talks about family, public service, commitment to community, life balance, faith, etc. It is short but to the point and has guided us well.

At some point, you will have someone more senior than you who says you must do A before B and then C. My advice: ignore them. Choose your own path. During my journey, I was encouraged to go down a traditional academic path. I did not do it. Yet, somehow, I was elected to the National Academy of Medicine before I turned 40. It was poignant because it was almost the only accomplishment that my father (a PhD scientist), who passed away before I was elected, would have understood.

So please, decide on your criteria and mission for career and life. Write them down, share them if you wish. Then follow them! Passionately! When things are going well, review them. Are you still aligned with what is important to you? When you are at a crossroads to make a decision, review them again. They should help guide your choice.

I often get asked "what keeps me up at night?" Honestly, nothing as I fall asleep in 10 seconds or less. But if something did, it is the fact that I am always worried that someone is falling through the cracks and getting suboptimal care. We must continue to strive to build a more highly reliable health system that delivers better quality, lower costs, and exceptional experience to all people. We cannot do that without great leaders. So, choose your own path, use your mission as a guide and lead focused on a better health system for all!

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Treatment of Pediatric Venous Thromboembolism

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GUIDELINE TITLE: American Society of Hematology 2018 Guidelines for the management of venous thromboembolism: treatment of pediatric venous thromboembolism

DEVELOPER: The American Society of Hematology multidisciplinary subcommittee

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FUNDING SOURCE: American Society of Hematology

PRIOR VERSION: N/A

TARGET POPULATION: less than 18 years of age

Venous thromboembolism (VTE) occurs uncommonly in pediatrics, affecting 0.07-0.14 per 10,000 children.[1,2] Yet, in the last 20 years, the incidence of VTE in hospitalized children has increased dramatically to approximately 58 per 10,000 admissions.[3] This increase may be attributed to improved survival of very ill children, better diagnostic imaging modalities, and heightened awareness by managing physicians.[3] Randomized controlled trials are lacking in pediatric thrombosis, and clinical care is based on extrapolation of adult data and expert consensus guidelines.[4,5] In 2014, the American Society of Hematology (ASH) sought to develop comprehensive guidelines on thrombosis. The pediatric VTE treatment guideline is one of six published to date.

RECOMMENDATIONS FOR THE HOSPITALIST

The following are five selected guideline recommendations thought most relevant to pediatric hospitalists. Three focus on the central venous access device (CVAD), since it is the most common risk factor for pediatric VTE.[1] Recommendations were graded as "strong" if most providers, patients, and policy makers agreed with the intervention and if it was supported by credible research. Conditional recommendations had less uniform agreement with an emphasis on individualized care and weighing patients' values and preferences.[6]

Recommendation 1. It is recommended that pediatric patients receive anticoagulation, versus no anticoagulation, for symptomatic VTE (evidence quality: low certainty; recommendation strength: strong).

There is strong indirect data in adults that symptomatic VTE requires treatment, with limited direct evidence in children. As VTE occurs most commonly in ill, hospitalized children with the potential for VTE to be life threatening, the benefit was felt to justify the strong recommendation despite low-quality evidence.

The primary benefit of anticoagulation in children with symptomatic VTE is the prevention of progressive or recurrent thrombosis with high morbidity and the prevention of life-threatening VTE. The greatest potential harm from the use of anticoagulation, particularly in very ill children, is the risk for major bleeding.[4]

Recommendation 2. Children with asymptomatic VTE can be managed with or without anticoagulation (evidence quality: poor; recommendation strength: conditional).

The panel focused on the unique features of pediatric VTE related to the heterogeneity in both the site and pathophysiology of VTE in children, such as age, presence of a CVAD, and comorbidities. There is little certainty that treating asymptomatic VTE is beneficial in the same way that treating symptomatic VTE would be in preventing recurrent thrombosis and embolization.

Until better evidence is available to guide care, the primary benefit of this recommendation is individualization of care related to each patient's risk-benefit profile and parental preferences.

Potential problems with using this recommendation include the cost of anticoagulant drugs and major bleeding if anticoagulation is used. Potential problems with not using anticoagulation would be progressive or recurrent thromboembolism. Close monitoring of children with VTE—regardless of whether anticoagulation is prescribed—is warranted.

Pediatric Patients with Symptomatic CVAD-Related Thrombosis

Recommendations three through five pertain to CVAD-associated thrombosis, so they are reviewed together.

Recommendation 3. No removal of a functioning CVAD is suggested if venous access is still required (evidence quality: low certainty; recommendation strength: conditional).

Recommendation 4. It is recommended to remove a nonfunctioning or unneeded CVAD (evidence quality: low certainty; recommendation strength: strong).

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Recommendation 5. It is suggested to delay CVAD removal until after initiation of anticoagulation (days), rather than immediate removal if the CVAD is nonfunctioning or no longer needed (evidence quality: low certainty; recommendation strength: conditional).

CVAD is the most common precipitating factor for pediatric VTE, particularly in neonates and older children.[1] Based on limited direct and indirect observational studies, there is low evidence of benefit for CVAD removal, but high-quality indirect evidence of harm and high cost, which the panel felt justified the strong recommendation for removing an unneeded or nonfunctioning line. If ongoing care can be safely administered without central access, removing the thrombosis stimulus is recommended. The guideline suggests keeping a functioning CVAD in a patient who requires ongoing venous access and placing high value on avoiding new line insertion when access sites may be limited to avoid the potential thrombogenic effect of new line placement.

In the limited direct and indirect observational studies identified, the optimal timing of CVAD removal is uncertain. Given the potential risk of emboli leading to pulmonary embolism or stroke, prior publications have suggested delaying removal until after three to five days of anticoagulation, particularly in children with known or potential right-to-left shunts.[4] The risk of infection and bleeding with anticoagulation prior to CVAD removal was considered small by the panel. This recommendation is primarily based on the panel's anecdotal experience and first principles, which is a limitation.

CRITIQUE

Methods in Preparing Guideline. The panel included pediatric experts with clinical and research expertise in the guideline topic, including nine hematologists, one intensivist, one cardiologist, one hematology pharmacist, and one anticoagulation nurse practitioner. It also included two methodologists with evidence appraisal and guideline development expertise, as well as two patient representatives.

The panel brainstormed and prioritized questions to be addressed and selected outcomes of interest for each question. The McMaster University GRADE Centre vetted and retained researchers to conduct or update systematic evidence reviews and coordinate the guideline development using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach.[6] For each guideline question, the results of systematic reviews were summarized in GRADE Evidence-to-Decision tables. The evidence quality was categorized into four levels ranging from very low to high. For each recommendation developed, the panel agreed on the evidence quality, balance of benefits and harms of compared management options with consideration of resource use, and inferences regarding the potential associated values and preferences. The panel addressed 26 questions, which generated 30 recommendations.

Draft recommendations were made available online for review by stakeholders, including allied organizations, medical professionals, patients, and the public. Revisions were made to address pertinent submitted comments, but the recommendations were not changed. After approval by ASH, the guideline was subjected to peer review by *Blood Advances*.

Sources of Potential Conflict of Interest or Bias. The guideline was developed and funded by ASH. All participants' conflicts of interest were managed according to ASH policies based on recommendations of the Institute of Medicine and the Guideline International Network. A majority of the guideline panel had no conflicts. During deliberations, panelists with direct financial interests were recused from making judgments about relevant recommendations. The McMaster University-affiliated researchers had no conflicts.

Generalizability. While this guideline included 30 recommendations, the ones highlighted apply to the most commonly seen pediatric VTE cases in hospital medicine. ASH emphasized that these guidelines should not be construed as the standard of care, but as a guide to help clinicians make treatment decisions for children with VTE and to enable them to individualize care when needed. The greatest limitation of this guideline is the lack of strong direct supporting evidence in pediatric VTE management.

AREAS IN NEED OF FUTURE STUDY

Although there is increasing interest in pediatric VTE prevention and risk assessment,[7] there is currently limited evidence on the best ways to mitigate VTE risk or anticoagulation-associated major bleeding in hospitalized children. The relatively low incidence of VTE in children makes large randomized controlled trials difficult, but several are ongoing. The Evaluation of the Duration of Therapy for Thrombosis in Children (Kids-DOTT) multicenter, randomized trial will inform care on the optimal duration of anticoagulation in children with a transient provoking factor,[8] and several phase III studies are investigating the safety and efficacy of direct oral anticoagulants in children (NCT02234843, NCT02464969, NCT01895777, NCT02234843). These and future trials will better inform therapy in pediatric VTE.

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The Management of Anticoagulation for Venous Thromboembolism in the Hospitalized Adult

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Anticoagulation for patients with venous thromboembolism (VTE) is associated not only with considerable benefits, including prevention of pulmonary embolus and thrombus extension, but also with potential significant risks, such as life-threatening bleeding.[1] Hospitalized patients may require anticoagulation to treat new VTE or for secondary prevention of prior events. Hospital admission is a high-risk time for anticoagulation control.[2] Additionally, anticoagulation has become an increasingly complex decision as the number of therapeutic agents on the market has significantly increased, coupled with medication interactions and dosing intricacies. Management is multifaceted and associated with wide variation in practice patterns.[3] Thus, further evidence-based guidance for providers is necessary for the care of the hospitalized patient with VTE.

KEY RECOMMENDATIONS FOR THE HOSPITALIST

The following are 16 selected guideline recommendations most relevant to adult hospitalists.[4] Recommendations were graded as "strong" if most individuals should follow the recommended course of action and "conditional" if different choices are appropriate for different patients.

Initial Anticoagulant Dosing, Monitoring, and Medication Interactions

(for all recommendations–evidence quality: low certainty; recommendation strength: conditional)

Recommendation 1. In obese patients receiving low molecular weight heparin (LMWH), determine the initial dose based on actual body weight rather than a fixed or "capped" maximum dose.

Recommendation 2. For obese patients or those with renal dysfunction receiving LMWH, avoid dosing based on serum antifactor Xa levels. Instead, adjust dosing based on product labeling, with appropriate dose reduction in patients with chronic kidney disease.

Recommendation 3. For patients receiving direct oral anticoagulant (DOAC) therapy, avoid measuring the anticoagulation effect during management of bleeding as there is no evidence to support a beneficial effect, and it may result in a delay in treatment.

Recommendation 4. For patients requiring administration of inhibitors or inducers of P-glycoprotein or cytochrome P450 enzymes, use LMWH or vitamin K antagonists (VKA) rather than a DOAC.

Recommendation 5. When transitioning from a DOAC to a VKA, the medications should overlap until the international normalized ratio (INR) is therapeutic instead of bridging with a heparin agent.

Recommendations for Ongoing Outpatient Monitoring upon Discharge from the Hospital

Recommendation 6. Use point-of-care INR testing by patients at home, with self-adjustment of VKA dose (evidence quality: low certainty; recommendation strength: strong).

Recommendation 7. Patients should be referred for specialized anticoagulation management rather than to their primary care provider (PCP) (evidence quality: very low certainty; recommendation strength: conditional).

Recommendation 8. Supplementary education, in addition to basic education, should be made available to patients to help improve outcomes (evidence quality: very low certainty; recommendation strength: conditional).

Hospitalists are often responsible for the coordination of care upon discharge from the hospital, including discharge teaching, subspecialty referrals, and determination of patient suitability for home monitoring and dose adjustment. The follow-up plan may depend on local systems and access. A PCP can manage anticoagulation if performed in a systematic and coordinated fashion.[5]

Recommendations for Patients on Anticoagulation Undergoing Procedures

Recommendation 9. For patients with a low or moderate risk of recurrent VTE on VKA therapy undergoing procedures, periprocedural bridging with heparin or LMWH should be avoided. This excludes patients at high risk for recurrent VTE, defined as those with recent VTE (<3 months); having a known thrombophilic abnormality such as antiphospholipid syndrome, protein C/S deficiency, or antithrombin deficiency; or high-risk patient populations by expert consensus and practice guidelines[4,6] (evidence quality: moderate certainty; recommendation strength: strong).

Recommendation 10. For patients on DOACs undergoing procedures, measurement of the anticoagulation effect of the

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DOAC should be avoided (evidence quality: very low certainty; recommendation strength: conditional).

Recommendations for Patients on Anticoagulation Suffering from Supratherapeutic Levels or Bleeding Complications

(for all recommendations–evidence quality: very low certainty; recommendation strength: conditional)

Recommendation 11. If a patient on VKA therapy has an INR between 4.5 and 10 *without* clinically relevant bleeding, the use of vitamin K therapy can be avoided in favor of temporary cessation of VKA alone.

Recommendation 12. If a patient on VKA therapy has life-threatening bleeding, four-factor prothrombin complex concentrate (PCC) should be used in addition to the cessation of VKA therapy and initiation of vitamin K therapy, over the use of fresh frozen plaza, because of the ease of administration and minimal risk of volume overload.

Recommendation 13. If a patient has life-threatening bleeding on a Xa inhibitor, the panel recommends discontinuation of the medication and the option to administer either PCC or recombinant coagulation factor Xa, as there have been no studies comparing these two strategies.

Recommendation 14. If life-threatening bleeding occurs in a patient on dabigatran, idarucizumab should be administered, if available.

Recommendation 15. In patients with bleeding while on heparin or LMWH, protamine should be administered.

Recommendation 16. Following an episode of life-threatening bleeding, anticoagulation should be resumed within 90 days, provided that the patient is at moderate to high risk for recurrent VTE, is not at high risk for recurrent bleeding, and is willing to continue anticoagulation.

CRITIQUE

Methods in Preparing Guidelines

The panel was funded by the American Society of Hematology (ASH), a nonprofit medical specialty society.[4] The panel is multidisciplinary, including physicians and providers as well as patient representatives, and is supported by the McMaster University GRADE Center, which conducted new and updated systematic reviews of the evidence according to the "Cochrane Handbook for Systematic Reviews of Interventions." The panel members agreed on 25 recommendations and two good practice statements. The recommendations were made available to external review by stakeholders and addressed. Comments made by 10 individuals or organizations were subsequently incorporated.

Sources of Potential Conflict of Interest

Panel members, other than patient representatives, did not receive funding, and the majority of the panel had no conflicts of interest to report. Given the minimal influence of outside parties including pharmaceutical companies, and the wide diversity of opinions sought in the creation of the guidelines, concern for conflict of interest is low.

Generalizability

These guidelines assume that the decision to anticoagulate a patient, and which agent to use, has already been made and thus do not offer further guidance on this decision. These guidelines also do not address optimal choices for anticoagulation in specific patient populations, such as patients with cancer. They are limited in scope to exclude the treatment of specific thromboembolic disease processes such as subsegmental pulmonary emboli, superficial venous thrombus, or distal vein thrombosis. Unfortunately, challenging decisions made by hospitalists frequently fall into one of these categories. Coincident with these guidelines, ASH introduced comprehensive guidelines to support basic diagnostic decisions.[7]

AREAS IN NEED OF FUTURE STUDY

More evidence is needed to better understand optimal monitoring practices for patients on anticoagulation therapy, including the ideal INR monitoring frequency for patients on VKA therapy. Additionally, there is a need to better understand the difference in clinical outcomes and resources utilization when care is provided by an anticoagulation specialist as compared with a PCP. Finally, while guidelines suggest that anticoagulation should be resumed within 90 days of a life-threatening bleed, there is a need to better understand the optimal timing of a restart, as well as the patient factors to be considered in this decision.

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Past is Prologue

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

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A 56-year-old Japanese man with a history of renal transplantation 20 years prior presented to the emergency department (ED) with two months of dyspnea on exertion and one day of fever and chills. The patient was in his usual state of health until two months prior to presentation, when he gradually noticed shortness of breath after sustained or effortful physical activities. The dyspnea improved with rest. Over the following two months, he noticed that the shortness of breath came on with lesser degrees of exertion, such as walking 100 meters. One day before presentation, he developed a fever of 39°C and chills at home, which prompted him to seek ED care. He denied chest pain, cough, leg swelling, or paroxysmal nocturnal dyspnea.

The differential diagnosis of exertional dyspnea progressing over several months includes cardiac, pulmonary, hematologic, and neuromuscular conditions. The patient's history of renal transplantation prompts consideration of worsening indolent pneumonia (eg, *Aspergillus*, cytomegalovirus [CMV], or *Pneumocystis* pneumonia), allograft dysfunction with volume overload, recrudescence of the underlying disease that incited renal failure earlier in life (eg, vasculitis), or a late-onset posttransplantation lymphoproliferative disorder (PTLD). Additionally, acute fever in an immunocompromised patient immediately raises suspicion for infection (eg, pneumonia, enteritis, or urinary tract infection). At this point, it is difficult to know whether the subacute-to-chronic exertional dyspnea and the acute fever are consequences of the same disease or separate, potentially overlapping, processes.

His past medical history was significant for end-stage renal disease due to membranoproliferative glomerular nephropathy (MPGN), for which living, related-donor kidney transplantation was performed 20 years earlier. He also had type 2 diabetes mellitus, hypertension, and basal cell carcinoma of the face, which had been resected three years prior without spread or recurrence. He had no known allergies. Medications included prednisolone 15 mg daily, azathioprine 100 mg daily, and cyclosporine 100 mg daily, as well as amlodipine and candesartan. He lived in Japan with his wife and children. He denied any animal or environmental exposures. He did not smoke cigarettes or drink alcohol and had not traveled recently. His father had diabetes mellitus.

Recrudescence of an underlying autoimmune condition that may have incited MPGN earlier in life is unlikely while taking an immunosuppressive regimen consisting of prednisolone, azathioprine, and cyclosporine. However, these medications do increase susceptibility to infections, lymphoma, and skin cancers. Though he is immunocompromised, the patient is not on prophylaxis for *Pneumocystis* pneumonia (PCP). PCP in HIV-negative patients is associated with recent glucocorticoid exposure and typically follows an acute-to-subacute course with hypoxemia and respiratory distress. Though the risk of PCP infection is considered highest in the early posttransplantation period (when immunosuppression is most intense), many cases are diagnosed years after transplantation among patients no longer on prophylaxis. The patient has type 2 diabetes mellitus and hypertension, which are known complications of calcineurin inhibitor and steroid therapy and increase the risk of cardiovascular disease. Cardiovascular disease is a major cause of death among renal transplant recipients. Exertional dyspnea may be the presenting symptom of coronary artery disease.

On physical examination, the patient was alert, oriented, and in no acute distress. His temperature was 38.5°C, blood pressure 120/60 mm Hg, heart rate 146 beats per minute, respiratory rate 18 breaths per minute, and oxygen saturation 93% while breathing ambient air. The conjunctiva were normal without pallor or icterus. There was no cervical lymphadenopathy. Cardiac examination revealed tachycardia with a regular rhythm, normal S1 and S2, and no murmurs, rubs, or gallops. Jugular venous pressure was not elevated, and there was no lower extremity edema. Lungs were clear to auscultation bilaterally. The abdomen was soft, nontender, and nondistended. There was no tenderness over the transplanted kidney and no hepatosplenomegaly.

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Dyspnea, fever, and tachycardia may be the sole manifestations of pneumonia in solid organ transplant recipients. The absence of cough or adventitious breath sounds does not eliminate concern for pneumonia. Pathogens that cause indolent pneumonia in immunocompromised patients include viruses (such as typical respiratory viruses and CMV), bacteria (typical organisms, *Nocardia*, *Rhodococcus*), and mycobacteria. Fungal causes include *Aspergillus*, *Candida*, *Cryptococcus*, *Pneumocystis*, and endemic mycoses. A detailed environmental history should be taken, and providers should ascertain which fungal diseases are endemic in the patient's region of residence. There are no examination features suggesting hypervolemia or anemia. Although there is no hepatosplenomegaly or lymphadenopathy, PTLD often involves extranodal tissues, including the lungs. The incidence of PTLD is highest in the 12 months following transplantation, but it may occur at any time in the posttransplantation course. A complete blood count, comprehensive metabolic panel, lactate dehydrogenase (LDH), and blood and sputum cultures are indicated, along with computed tomography (CT) of the chest.

The leukocyte count was 3,500 cells/mm^3, the hemoglobin level 9.0 g/dL, mean corpuscular volume 102 fL, and the platelet count 137,000 cells/mm^3. The sodium level was 130 mEq/L, potassium 4.6 mEq/L, blood urea nitrogen 41 mg/dL, and creatinine 3.5 mg/dL. These complete blood count and serum electrolyte results were unchanged from the patient's baseline values. The serum LDH level was 1,895 IU/L (normal range, 115-245 IU/L). The serum ferritin was 2,114 ng/mL (normal range, 13-277 ng/mL). A chest radiograph revealed diffuse, airspace-filling opacities in the bilateral lung bases. The urinalysis was normal. The patient was admitted and started empirically on intravenous ceftriaxone for potential bacterial pneumonia.

Chronic pancytopenia may result from azathioprine or cyclosporine use, marrow suppression or infiltration by a multisystem disease, or nutritional deficiency. Hemophagocytic lymphohistiocytosis (HLH) triggered by infection, a rheumatologic condition, acquired immunodeficiency, or malignancy can present with fevers, pancytopenia, and elevated ferritin, while splenomegaly may be absent. The euvolemic state, baseline creatinine level, and normal urinalysis argue against allograft dysfunction. The elevated serum ferritin nonspecifically confirms systemic inflammation. LDH, an intracellular enzyme involved in the bidirectional conversion of lactate to pyruvate, is expressed across tissue types. Elevated serum LDH attests to cell destruction, in this case potentially from lung infection (such as PCP) or malignancy (such as PTLD). At this point, the differential diagnosis of fever and pulmonary infiltrates in this patient remains broad.

Azathioprine and cyclosporine were stopped. The patient remained febrile despite the administration of intravenous antibiotics. His hypoxia worsened with an oxygen saturation of 90%-93% on 5 L/min of supplemental oxygen administered by nasal cannula. Noncontrast chest CT obtained on the second hospital day revealed ground-glass opacities in the bilateral lung bases. Blood, sputum, and urine cultures were sterile. As empiric therapies, ganciclovir was started for CMV infection, ciprofloxacin added for atypical pneumonia, and trimethoprim-sulfamethoxazole added for *Pneumocystis* infection.

These chest imaging findings help prioritize the differential diagnosis. Bibasilar ground-glass opacities are evident, while pulmonary masses, nodules, cavitation, adenopathy, and pleural effusions are absent. The differential diagnosis of multifocal ground-glass opacities on chest imaging includes infectious pneumonia, chronic interstitial lung disease, acute alveolar conditions (eg, cardiogenic pulmonary edema, acute respiratory distress syndrome, diffuse alveolar hemorrhage), or other pathologies (eg, drug toxicity, bronchoalveolar carcinoma, cryptogenic organizing pneumonia).

Infectious pneumonia is the principal concern. A diagnosis of PCP could be unifying, given dyspnea, progressive respiratory failure with hypoxia, and elevated LDH in an immunocompromised patient who is not prescribed PCP prophylaxis. The bilateral lung infiltrates and the absence of thoracic adenopathy or pleural effusions are characteristic of PCP as well. However, caution should be exercised in making specific infectious diagnoses in immunocompromised hosts on the basis of clinical and imaging findings alone. There can be overlap in the radiologic appearance of various infections (eg, CMV pneumonia can also present with bilateral ground-glass infiltrates, with concurrent fever, hypoxia, and pancytopenia). Additionally, more than one pneumonic pathogen may be implicated (eg, acute viral pneumonia superimposed on indolent fungal pneumonia). Polymerase chain reaction (PCR) analysis of respiratory secretions for viruses, serum PCR and serologic testing for herpes viruses, and serum beta-D-glucan and galactomannan assays are indicated. Serum serologic testing for fungi and bacteria such as *Nocardia* can be helpful, though the negative predictive values of these tests may be reduced in patients with impaired humoral immunity. Timely bronchoalveolar lavage (BAL) with microbiologic and PCR analysis and cytology is advised.

Fever, elevated LDH, cytopenias, and pulmonary infiltrates also raise suspicion for an underlying hematologic malignancy, such as PTLD. However, pulmonary PTLD is seen more often in lung transplant recipients than in patients who have undergone transplantation of other solid organs. In kidney transplant recipients, PTLD most commonly manifests in the allograft itself, gastrointestinal tract, central nervous system, or lymph nodes; lung involvement is less common. Chest imaging in affected patients may reveal nodular or reticulonodular infiltrates of basilar predominance, solitary or multiple masses, cavitating or necrotic lesions, and/or lymphadenopathy. In this patient who has undergone renal transplantation, late-onset PTLD with isolated pulmonary involvement, with only ground-glass opacities on lung imaging, would be an atypical presentation of an uncommon syndrome.

Despite empiric treatment with antibiotics and antiviral agents, the patient's fever persisted. His respiratory rate

increased to 30 breaths per minute. His hypoxia worsened, and he required nasal cannula high-flow oxygen supplementation at 30 L/min with a fraction of inspired oxygen (FiO_2) of 40%. On the fifth hospital day, contrast CT scan of the chest and abdomen showed new infiltrates in the bilateral upper lung fields as well as an area of low density in the tail of the pancreas without a focal mass (Figure 1). At this point, BAL was performed, and fluid PCR analysis returned positive for *Pneumocystis jirovecii*. CMV direct immunoperoxidase staining of leukocytes with peroxidase-labeled monoclonal antibody (C7-HRP test) was positive at five cells per 7.35 × 10^4 peripheral blood leukocytes. The serum Epstein-Barr virus (EBV) viral capsid antigen (VCA) IgG was positive, while VCA IgM and EBV nuclear antigen IgG were negative. A bone marrow biopsy revealed mild hemophagocytosis. His serum soluble interleukin-2 (sIL2R) level was elevated at 5,254 U/mL (normal range, 122-496 U/mL). Given the BAL *Pneumocystis* PCR result, the dose of prednisolone was increased to 30 mg/day, and the patient's fever subsided. Supplemental oxygen was weaned to an FiO_2 of 35%.

These studies should be interpreted carefully considering the biphasic clinical course. After two months of exertional dyspnea, the patient acutely developed persistent fever and progressive lung infiltrates. His clinical course, the positive PCR assay for *Pneumocystis jirovecii* in BAL fluid, and the compatible lung imaging findings make *Pneumocystis jirovecii* a likely pathogen. But PCP may only explain the second phase of this patient's illness, considering its often-fulminant course in HIV-negative patients. To explain the two months of exertional dyspnea, marrow hemophagocytosis, pancreatic abnormality, and perhaps even the patient's heightened susceptibility to PCP infection, an index of suspicion should be maintained for a separate, antecedent process. This could be either an indolent infection (eg, CMV or *Aspergillus* pneumonia) or a malignancy (eg, lymphoma or PTLD). Completion of serum serologic testing for viruses, bacteria, and fungi and comprehensive BAL fluid analysis (culture, viral PCR, and cytology) is recommended.

A CMV antigenemia assay returned positive, suggesting prior CMV infection. However, to diagnose CMV pneumonia, the virus must be detected in BAL fluid by PCR or cytologic analysis. CMV infection has been associated with cytopenias, HLH, pancreatic infiltration, and an increased risk for fungal infections and EBV-related PTLD. CMV infection could explain the first phase of this patient's illness. Serum and BAL PCR for CMV are advised. Meanwhile, EBV testing indicates prior infection but does not distinguish between recent or more distant infection. EBV has been implicated in the pathophysiology of PTLD, as EBV-infected lymphoid tissue may proliferate in a variety of organs under reduced T-cell surveillance. EBV infection or PTLD with resulting immunomodulation may pose other explanations for this patient's development of PCP infection. Cytologic analysis of the BAL fluid and marrow aspirate for evidence of PTLD is warranted. Finally, CMV, EBV, and PTLD have each been reported to trigger HLH. Though this patient has fevers,

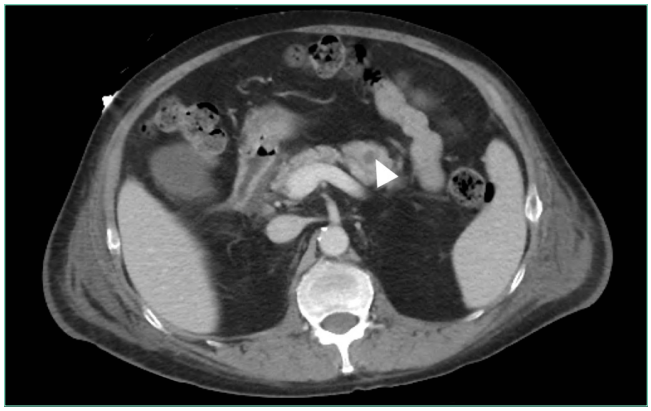

FIG 1. Selected axial image from a CT of the abdomen showing a low-density area in the tail of the pancreas (arrowhead). There were no other masses or lymphadenopathy.

mild marrow hemophagocytosis, elevated serum ferritin, and elevated serum IL-2 receptor levels, he does not meet other diagnostic criteria for HLH (such as more pronounced cytopenias, splenomegaly, hypertriglyceridemia, hypofibrinogenemia, and low or absent natural killer T-cell activity). However, HLH may be muted in this patient because he was prescribed cyclosporine, which has been used in HLH treatment protocols.

On the 11th hospital day, the patient developed hemorrhagic shock due to massive hematemesis and was transferred to the intensive care unit. His hemoglobin level was 5.9 g/dL. A total of 18 units of packed red blood cells were transfused over the following week for ongoing gastrointestinal bleeding. The serum LDH level increased to 4,139 IU/L, and the ferritin level rose to 7,855 ng/mL. The EBV copy level by serum PCR returned at 1 × 10^6 copies/mL (normal range, less than 2 x 10^2 copies/mL). The patient was started on methylprednisolone (1 g/day for three days) and transitioned to dexamethasone and cyclosporine for possible EBV-related HLH. Ceftazidime, vancomycin, trimethoprim-sulfamethoxazole, and ciprofloxacin were administered. Amphotericin-B was initiated empirically for potential fungal pneumonia. Ganciclovir was continued. However, the patient remained in shock despite vasopressors and transfusions and died on the 22nd hospital day.

The patient deteriorated despite broad antimicrobial therapy. Laboratory studies revealed EBV viremia and rising serum LDH. Recent EBV infection may have induced PTLD in the gastrointestinal tract, which is a commonly involved site among affected renal transplant patients. Corticosteroids and stress from critical illness can contribute to intestinal mucosal erosion and bleeding from a luminal PTLD lesion. Overall, the patient's condition was likely explained by EBV infection, which triggered HLH and gastrointestinal PTLD. The resulting immunomodulation increased his risk for PCP infection beyond that conferred by chronic immunosuppression. It is still possible that he had concomitant CMV pneumonia, *Aspergillus* pneumonia, or even pulmonary PTLD, in addition to the proven PCP diagnosis.

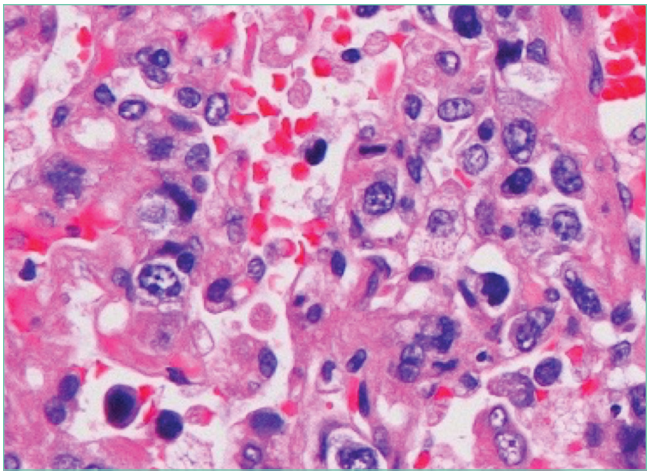

FIG 2. Histologic section (Hematoxylin and Eosin staining) obtained at autopsy from the right upper lung lobe, showing diffuse alveolar damage and a lymphoid infiltrate characterized by large, atypical lymphoid cells.

An autopsy was performed. Atypical lymphocytic infiltration and diffuse alveolar damage were shown in the right upper lobe (Figure 2). EBV RNA-positive atypical lymphocytes coexpressing CD20 were demonstrated in multiple organs including the bone marrow, lungs, heart, stomach, adrenal glands, duodenum, ileum, and mesentery (Figure 3). This confirmed the diagnosis of an underlying EBV-positive posttransplant lymphoproliferative disorder. Serum and BAL CMV PCR assays returned negative. Neither CMV nor *Aspergillus* was identified in autopsy specimens.

COMMENTARY

A broad differential diagnosis should be considered when acute fever develops in a patient who has undergone solid organ transplantation. Causes may include opportunistic and nonopportunistic infections as well as noninfectious etiologies such as malignancy, organ rejection, inflammatory conditions, and medication toxicity.[1,2] As the discussant noted, more than one infection, or both infection and malignancy, can coexist in immunocompromised patients. For example, while viral pathogens such as EBV, CMV, and respiratory syncytial virus can cause illness due to direct tissue infection, they can also exert indirect effects in transplant recipients: acting as cofactors for and enabling other infections by causing immunosuppression (eg, *Aspergillus* or PCP developing after CMV infection), triggering graft rejection by upregulating proinflammatory cytokines, and inducing oncogenesis (eg, EBV-related PTLD).[1,3-5]

PTLD is a rare but serious complication of solid organ transplantation and immunosuppression. Most cases are driven by EBV infection and subsequent transformation of infected lymphoid tissue in a variety of organs in the context of reduced T-cell surveillance.[6] The incidence of PTLD varies based on the organ transplanted, ranging from 0.8%-2.5% in those who have undergone renal transplantation to 1.0%-5.5% in liver transplant recipients and 3.0%-10% in lung transplant recipients.[3] The incidence has increased over the past decade. This may be due to a greater number of solid organ transplantations being performed, aging of the transplant donor/recipient population, new immunosuppressive regimens, and improved PTLD diagnosis due to superior diagnostic tools and clinician awareness.[3] However, the mortality rate among solid organ transplant recipients with PTLD remains high, ranging from 40% to 70%.[6]

Risk factors for PTLD include a greater intensity of T-cell immunosuppression,[7] history of pretransplant malignancy, recipient EBV seronegativity and donor seropositivity, and younger age at the time of transplantation.[8-10] EBV-related PTLD incidence in solid organ transplant recipients is greatest in the early posttransplantation course (the period of most intense immunosuppression) with over 80% of cases occurring in the first posttransplant year.[11]

A high index of suspicion for PTLD is warranted in any solid organ transplant recipient who presents with constitutional symptoms, adenopathy, or cytopenias. Clinical suspicion of PTLD can be informed by risk factors, constitutional symptoms, elevated serum LDH, a detectable or rising serum EBV viral load, and radiologic adenopathy or visceral tissue infiltration.[12] The clinical presentation of PTLD is heterogeneous and varies in accordance with the organs affected. Extranodal involvement, such as pulmonary, gastrointestinal, and bone marrow involvement, is more common in PTLD than in other types of lymphoma.[13] In this patient, the cytopenias, elevated serum LDH level, lung infiltrates, and radiologic pancreatic tail abnormality served as early clues to the presence of underlying PTLD.

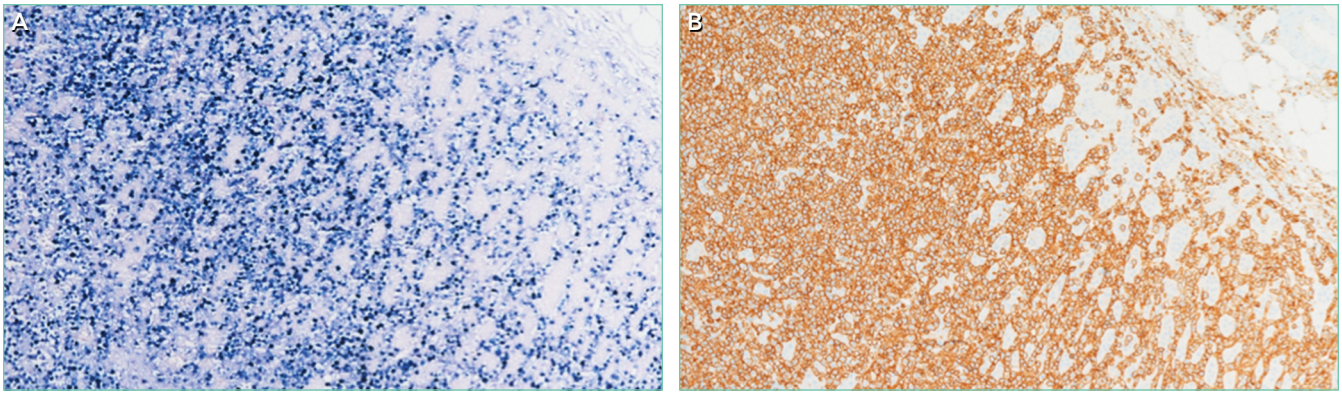

FIG 3. Immunohistochemical staining of tissue obtained from adrenal gland biopsies identified both EBV RNA-positive (Panel A) and CD20-positive lymphocytes (Panel B).

The standard approach to diagnosing PTLD is biopsy of a suspicious lesion (adenopathy or an infiltrated visceral organ) with histopathological examination. Pathology may demonstrate distorted tissue architecture, clonal lymphocytes, or EBV-positive lymphocytes.[14] Conventional CT is the most commonly used imaging modality to detect adenopathy or tissue infiltration related to PTLD,[3] though 18F-fluorodeoxyglucose position-emission tomography (FDG-PET) is also used. Although FDG-PET has high diagnostic accuracy, with an overall sensitivity of 89% and specificity of 89%, false-negative results have been reported, particularly in cases of early PTLD lesions and diffuse large B-cell lymphoma.[15] The majority of patients with EBV-associated PTLD demonstrate significant elevations in the serum EBV viral load compared with immunosuppressed controls without PTLD.[16] An elevated EBV viral load can support a diagnosis of PTLD, though the absence of EBV viremia does not rule it out.[17] Some transplant centers perform post-transplantation monitoring of the serum EBV viral load to aid in PTLD risk assessment and early diagnosis.

Management of PTLD is patient-specific and may involve reduction of immunosuppressive therapy, rituximab, chemotherapy, surgical excision, and/or radiation.[13] Reduction of immunosuppression is the cornerstone of treatment.[18] In patients who do not respond to the reduction of immunosuppression, rituximab and immunochemotherapy are second-line treatment options. A prospective, multicenter phase 2 trial (the PTLD-1 trial) demonstrated a complete response rate of 40% among patients with PTLD managed with rituximab.[19]

In summary, this case illustrates the importance of maintaining a broad differential diagnosis when acute fever develops in a patient who has undergone solid organ transplantation. The presence of more than one condition should be considered when the clinical presentation cannot be explained by a single diagnosis, as infections and malignancies can coexist in immunocompromised hosts. This case also highlights an unusual clinical presentation of PTLD, which was heralded mainly by its immunomodulatory effects rather than by compatible symptoms or obvious mass lesions.

Carefully reviewing the patient's medical history and understanding how it sets the stage for the present illness is an essential step in clinical problem solving, because what is past is prologue.

TEACHING POINTS

- Fever in solid organ transplant recipients should prompt consideration of a broad differential diagnosis, including infection, malignancy, organ graft rejection, autoimmune disease, and medication toxicity.
- PTLD is a rare but serious complication of organ transplantation. Most cases are driven by EBV infection and transformation of infected lymphocytes in a variety of organs in the context of reduced T-cell surveillance. The clinical presentation can be heterogeneous and varies depending on the organs and tissues involved.
- More than one infection, or both infection and malignancy, can coexist in organ transplant recipients. Viral pathogens can exert direct pathologic effects on tissue but can also exert indirect effects, such as contributing to opportunistic infection susceptibility, graft rejection, and oncogenesis.

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Counting the Ways to Count Medications: The Challenges of Defining Pediatric Polypharmacy

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Polypharmacy, the practice of taking multiple medications to manage health conditions, is common for children. Many children today have a higher burden chronic illness and an increasing number of pharmaceuticals—often delivered in various doses throughout the day. Polypharmacy has been linked to a variety of pediatric and adult outcomes, including medication errors and readmission.[1-3] Consequently, the Society of Hospital Medicine recognizes polypharmacy as a risk factor for readmission for adult populations.[4] These adverse outcomes are related to both the human elements of polypharmacy (eg, cognitive burden, adherence) and the pharmacologic elements, including drug–drug interactions. For many children, the safety implications of polypharmacy may be more consequential due to the reliance of multiple caregivers to administer medications, which requires additional coordination to ensure that medications are administered and not duplicated. Dual administration of the same medication by both parents is the most common reason for pediatric calls to Poison Control Centers.[5] Yet, there is a paucity of research in this area, with most of the pediatric literature focusing on the outpatient setting and specific populations, including epilepsy and mental health.[6-8]

How providers, patients, and families translate medication lists to counts of medications—and hence the burden of polypharmacy—is not clearly or consistently described. Often in studies of polypharmacy, researchers utilize medication claims data to count the number of medications a patient has filled from the pharmacy. However, in routine clinical practice, clinicians rarely have access to medication claims and thus rely on patient or family report, which may or may not match the list of medications in the patients' medical records.

Therefore, linking polypharmacy research to the pragmatic complexities of clinical care requires greater clarity and consistent application of concepts. At hospital discharge, families receive a list of medications to take, including home medications to resume as well as newly prescribed medications. However, not all medications are equally essential to patients' care regarding importance of administration (eg, hydrocortisone ointment versus an anticonvulsant medication). Patients, parents, and caregivers are ultimately responsible for determining which medications to prioritize and administer.

Although there is no standard numerical definition for how to identify polypharmacy, five medications is commonly considered the threshold for polypharmacy.[9] A recent review of the pediatric polypharmacy literature suggested a lower threshold, with any two concurrent medications for at least a day.[7] Yet, the best approach to "count" medications at hospital discharge is unclear. The simplest method is to tally the number of medications listed in the discharge summary. However, medications are sometimes listed twice due to different dosages administered at different times. Frequently, medications are prescribed on an as-needed basis; these medications could be administered routinely or very infrequently (eg, epinephrine for anaphylaxis). Over-the-counter medications are also sometimes included in discharge summaries and consideration should be given as to whether these medications count toward measures of polypharmacy. Over-the-counter medications would not be counted by a polypharmacy measure that relies on claims data if those medications are not paid by the insurer.

We sought consensus on how to count discharge medications through a series of informal interviews with hospitalists, nurses, and parents. We asked the seemingly simple question, "How many medications is this child on?" across a variety of scenarios (Figure). For panel A, all stakeholders agreed that this medication list includes two medications. All other scenarios elicited disagreement. For panel B, many people responded three medications, but others (often physicians) counted only clindamycin and therefore responded one medication.

For panel C, stakeholders were split between one (only topiramate), two (topiramate and rectal diazepam), and three medications (two different doses of topiramate, which counted as two different medications, plus rectal diazepam). Interestingly, one parent reflected that they would count panel C differently, depending on with whom they were discussing the medications. If the parent were speaking with a physician, they would consider the two different doses of topiramate as a single medication; however, if they were conveying a list of medications to a babysitter, they would consider them as two different medications. Finally, panel D also split stakeholders

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How many medications is this child on?

Panel A
Amoxicillin twice a day by mouth
Fluticasone twice a day by inhaler

Panel B
Clindamycin three times a day by mouth
Ibuprofen every 4 hours as needed by mouth
Acetaminophen every 4 hours as needed by mouth

Panel C
Topiramate 3 mL by mouth each morning
Topiramate 5 mL by mouth each evening
Diazepam by rectum as needed for seizure

Panel D
Oxycodone SR 20 mg twice a day
Oxycodone 5 mg every 4 hours as needed by mouth

FIG. Clinical scenarios where stakeholders were asked to count the number of medications*

*Seven scenarios were presented to stakeholder groups. Individuals had an opportunity to answer for themselves and then participated a facilitated discussion of the different answers and rationale. Two physician groups (each with ~10 participants), one parent group (with ~20 participants), and six discussions with individual bedside nurses informed this perspective.
Abbreviation: SR, sustained-release formulation.

between counting one and two medications, with some parents expressing confusion as to why the child would be prescribed the same medication at different times.

While our informal conversations with physicians, nurses, and families should not be construed as rigorous qualitative research, we are concerned about the lack of a shared mental model about the best way to count discharge polypharmacy. In reviewing the comments that we collected, the family voice stands out—physicians do not know how a parent or a caregiver will prioritize the medications to give to their child; physicians do not know whether families will count medications as a group or as separate entities. Although providers, patients, and families share a list of medications at discharge, this list may contain items not considered as "medications" by physicians.[10] Nevertheless, the medication list provided at discharge is what the family must navigate once home. One way to consider discharge polypharmacy would be to count all the medications in the discharge summary, regardless of clinicians' perceptions of necessity or importance. Electronic health record based tools should sum medications counts. Ultimately, further research is needed to understand the cognitive and care burden discharge polypharmacy places on families as well as understand this burden's relationship to safety and transition outcomes. Clinicians should recognize that the perceived care burden from polypharmacy will likely vary from family to family. Research is needed to develop and validate tools to assess family capacity and polypharmacy-related burden and to make shared decisions regarding medication prescribing and deprescribing[11,12] in this context.

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Waiting for Godot: The Quest to Promote Scholarship in Hospital Medicine

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Twenty years into the hospitalist movement, the proven formula for developing high-quality scholarly output in a hospital medicine group remains elusive. In this issue of the *Journal of Hospital Medicine*, McKinney et al. describe a new model in which an academic research coach—a PhD-trained researcher with 50% protected time to assist with hospitalist scholarly activities—is utilized to support scholarship.[1] Built on the premise that most hospitalist faculty do not have research training and many are embarking on their first academic project, the research coach was available to engage hospitalists at any stage of scholarship from conceptualizing an idea, to submitting one's first IRB, to data analysis, and grant and manuscript submission. This innovation (and the financial investment required) provides an opportunity to consider how to facilitate scholarship and measure its value in hospital medicine groups.

Academic institutions are built on the premise that scholarship—and research in particular—is of equal value to clinical care and teaching; a perspective that is commonly enshrined in promotion criteria that require scholarship for career advancement. While hospitalists are competent to begin clinical practice and transfer their knowledge to others at the conclusion of their residency, most are not prepared to lead research programs or create academic products from their clinical innovations, quality improvement, or medical education work. Yet, particularly for hospitalists who choose to practice in an academic setting, the leadership of their Section, Division, or Department may naturally expect scholarship to occur, similar to other clinical disciplines. In our experience as the directors of research and faculty development in our hospital medicine group, meeting this expectation requires recognizing that faculty development and scholarship development are intertwined and there must be an investment in both.

We believe that faculty development is required—but not sufficient—for the development of high-quality scholarship. In order for hospitalists to generate new knowledge in clinical, educational, quality improvement, and research domains, they must acquire a new skill set after residency training. These skills can be gained in different formats and time frames such as dedicated hospital medicine fellowships, internal faculty development programs, external programs (eg, Academic Hospitalist Academy), and/or individual mentorship. Descriptions of internal faculty development programs have unfortunately been limited to a single institutions with uncertain generalizability.[2,3] One could argue that faculty development may even be *more* important in hospital medicine than in clinical subspecialties given the relative youth of the field and the experience level of the entry-level faculty. Pediatric hospital medicine may be farthest along in faculty development and scholarship development after becoming a distinct subspecialty recognized by the American Board of Pediatrics and American Board of Medical Specialties; pediatric hospitalists must now complete fellowship training after residency before independent practice.[4] Importantly, completion of a scholarly product that advances the field is a required component of the pediatric hospital medicine fellowship curricular framework.[5] Regardless of what infrastructure a hospital medicine group chooses to build, there is a growing realization that faculty development must be firmly in place in order for scholarship to flourish.

In addition to junior faculty development, there is also a need for scholarship development to translate new skills into products of scholarship. For example, a well-published senior faculty member still may need statistical assistance and a midcareer hospitalist who leads quality improvement may struggle to write an effective manuscript to disseminate their findings. McKinney et al.'s innovation seems intended to meet this need, and the just-in-time and menu-style nature of the academic research coach resource is unique and novel. One can imagine how this approach to increasing scholarship productivity could be effective and utilized by busy junior, midcareer, and senior hospitalists alike. As the authors point out, this model attempts to mitigate the drawbacks that other models for enhancing hospitalist scholarship have faced, such as relying on physician scientists as mentors, holding works-in-progress or research seminars, or funding a consulting statistician. A well-trained scientist who meets hospitalists "where they are" is appealing when placed in the context of an effective faculty development program that enables faculty to take advantage of this resource. We hope that future evaluations of this promising innovation will include a comparison group to measure the effect of the academic research coach and demonstrate a return on the financial investment supporting the academic research coach.

Measuring return on investment requires defining the value of scholarship in hospital medicine. Some things that are easy to measure and have valence for traditional academic produc-

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tivity are captured in the McKinney manuscript: the number of abstracts, papers, and grants. Indirect costs from extramural funding may be particularly important for the financial "bottom line" of many hospitalist groups, which tend to be clinical cost centers in most academic institutions. However, other outcomes that are more challenging to measure may be equally or more important. Does investment in a model to support scholarly productivity lead to less burnout, higher retention, and greater professional satisfaction for academic hospitalists? Does this investment change group culture from "week on, week off" or "on service, off service" to one that has more balance in clinical and nonclinical pursuits?[6] How does investment in research development translate into national reputation, the ability to recruit outstanding candidates, or the number of hospitalist faculty who become interested in research careers? Measuring the impact of an academic research coach or other intervention on these factors might offer useful insights to drive further investment in hospitalist scholarship.

Measuring the value of scholarship in hospital medicine touches very near to the core of the value proposition of hospital medicine overall as a specialty. Without high-quality scholarship that demonstrates the influence of hospitalists in improving systems, leading change, educating learners, and advocating for the needs of our patients, why continue to invest in this model? We are struck every year at the Society of Hospital Medicine national conference about how much innovation hospitalists are leading – and how little is systematically evaluated or disseminated. In Beckett's "Waiting for Godot," Vladimir and Estragon talk about life and wait for Godot who, of course, never arrives. Instead of patiently waiting for more scholarship to arrive, we suggest that hospital medicine leaders follow the lead of McKinney et al. and take action by investing in it.

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Quantity, Quality, or Neither–Measuring the Effectiveness of Rounds

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Medicine has a rich history of attending-led rounds, with some iteration of this ritual occurring as far back as the 1600s.[1] In the early 1900s, the concept of "bedside rounds" was popularized by William Osler, who widely espoused their importance as a clinical and educational tool. Despite our best intentions, however, rounds today may be little reminiscent of the rounds of Osler's day. Recent investigations into the characteristics of rounds have specifically revealed a "shift in the format from the beside to conference rooms and hallways."[2] Most of our practices for rounding in the modern era are built on tradition and belief rather than evidence. The ecosystem of modern hospital care is dramatically different than that of Osler's day, and fundamental questions about the format, content, stakeholders, and processes of rounds remain. Perhaps the greatest and most needed change in rounding in recent years is the shift of rounds from a physician-centric activity to an activity that values the modern interprofessional hospital team. Ultimately, the very definition of "rounds" and the purpose they are meant to serve in the context of a dynamic and complicated hospital ecosystem has become increasingly complex and thus, difficult to assess and improve.

In this month's *Journal of Hospital Medicine*, Sang et al.[3] address this complexity by returning to basics and utilizing a novel approach to precisely measure the frequency and duration of a necessary (albeit insufficient) condition for interdisciplinary bedside rounding to occur: colocation of physician, nurse, and patient. Ultimately, their results provide a springboard to ask more complex and meaningful questions. Why, despite a recent culture shift prioritizing a return to bedside, is substantive physician and nurse colocation so persistently difficult to attain? How can we study outcomes of interdisciplinary bedside rounds if we cannot reliably facilitate their occurrence? What does "effective" rounding even mean? That is, what variables would be both meaningful and sensitive to changes in rounds?

After centuries of rounding, the medical community would be presumed to have perfected this art; however, we are instead left with more questions than answers. Prior research efforts have demonstrated the shifting of rounds away from the bedside, with bedside rounds occurring only 10%-40% of the time based on bias-prone survey data.[2,4] Interestingly, a study by Huang et al., designed specifically to increase implementation of interdisciplinary bedside rounds, showed a frequency of only 64%.[5] These studies are focused primarily on parameters such as patient and nursing satisfaction and did not include other important outcomes such as length of stay, readmission rates, diagnostic quality, patient engagement, or mortality.[2,4,6]

In Sang et al.,[3] the authors utilized a real-time locator system, namely, radiofrequency identification, to precisely track the physical workflow of both attending hospitalists and bedside nurses and then subsequently used the data obtained to measure the frequency and duration of colocation at the patient bedside. The authors defined a physician "rounding event" as the physician's presence in a single bed patient room for at least 10 seconds. The study revealed that colocation of physician and nurse (for at least 10 seconds) occurred in only 30% of all physician rounding events recorded. The duration of a physician rounding event was 5.68 minutes without nurse colocation and 9.56 minutes if a nurse was present. No difference in the frequency of physician-nurse overlap was observed between weekdays and weekends. Interestingly and not surprisingly, patient rooms located farther from the nursing station had a decreased likelihood of physician-nurse overlap.

A greater understanding of the medical community's inability to reliably implement interdisciplinary bedside rounding may be found by examining the ecosystem of inpatient medicine. Physicians and nurses function in an environment with increasingly complex patients, more stringent (and non-evidence-based) documentation requirements, the physical decoupling of patients and their clinical information, and, as Sang et al.[3] illuminate, complex geographical ward structures. As the rapidity with which patients are diagnosed and treated continues to escalate, physicians and nurses are also asked to attempt to squeeze an Oslerian-type rounding system into an ecosystem that is in overdrive. That the puzzle pieces do not fit should not be a surprise.

There is a risk that systems may implement interventions to "check the box" for interdisciplinary bedside rounding instead of seeking to change outcomes. How much time is time enough together at the bedside? Sang et al., among others, ponder whether a rounding duration of just under 10 minutes is enough.[3,6] However, Rothberg et al. demonstrated that increased *duration* of communication alone is not necessarily associated with increased patient satisfaction or nurse–physician agreement on plan of care,[7] suggesting that colocation and communication are necessary but not sufficient for true interdisciplinary patient care. The discordance between communication and understanding can potentially be explained by the varying agendas of the members of the interdisciplinary team during the same interaction.[8]

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Ultimately, the future of interdisciplinary bedside rounding, and rounding in general, remains uncertain. Potential areas for improvement and further study include patient regionalization,[3,5] tools to align agendas among stakeholders,[8] integrating recommendations for interdisciplinary communication,[9] and utilizing a common definition and taxonomy for study design.[10] These interventions may improve future study designs and outcomes. However, these interventions are small tweaks in a complex ecosystem, and the return on these interventions may eventually reach an asymptote. Perhaps the concept of rounding as we know it is broken beyond repair, and a more radical approach is needed: either the creation of a completely innovative shared mental model of acute care that acknowledges the complex environment of inpatient medicine, or a complete restructuring of the ecosystem itself. Nonetheless, the findings of Sang et al.[3] with respect to the ongoing difficulty of implementing interdisciplinary bedside rounding elucidate the need for innovation in study design and rounding implementation strategies; they also prompt us to ask—and answer—the complicated questions related to this integral component of our practice.

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Beyond Mortality: Improving Outcomes for Children Who Deteriorate in Inpatient Settings

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The past 20 years has seen an explosion of approaches to improve the recognition of children who deteriorate in the hospital. Early Warning Scores, Rapid Response Teams, Situational Awareness, and Parent-Triggered Activation systems are a few of the safety initiatives implemented worldwide. Many have an inherent face validity; for example, it would appear to be intuitive that highlighting the changes in physiology via a Pediatric Early Warning Score (PEWS) would enable staff to recognize a change in disease process and intervene accordingly. However, although mortality trends have been shown to diminish over time,[1] the evidence base supporting their impact has often been quite heterogeneous.[2,3] In particular, a recent international randomized control trial of a PEWS approach was found not to improve overall mortality.[4]

A major challenge with the evaluation of these patient safety systems is the reliance on mortality as an outcome measure. This is relatively rare, even in large tertiary institutions with complex patients and finding other proxy measures of quality of care are important. Hussain et al. have created a relatively easy to measure metric, an emergency transfer (ET). The benefit of the ET is its simplicity and transferability, which is described as follows:

> "Emergency Transfer (ET) is defined as any patient transferred to the ICU where the patient received intubation, inotropes, or three or more fluid boluses in the first hour after arrival or before transfer."[5]

All these components are easily extractable from written or electronic records and are representative of meaningful deterioration. Pressure on bed states, challenges with staff skill mix, and increasing parental expectation may all impact on decisions to transfer patients. The ET metric is relatively immune to these biases as its tight time definition separates it from the previous Bonafide et al.[6] measure (similar interventions but within a 12-hour window) as being centered on an abrupt critical change, rather than a potential drift toward deterioration. This makes the measure useful not only to an individual institution to measure the impact of an intervention but also internationally, as a comparison between institutions will not be influenced by health system differences.

The ET metric is important as Hussain et al. have demonstrated that it is associated with a worse outcome for the child both as a concrete outcome (increased mortality when it does occur) and as an experience (a longer stay in hospital). "*You can't improve what you can't measure*" is an old improvement maxim, and only by broadening our use of alternative metrics of care will we be able to understand which interventions will make a difference to patients. Certainly, evidence suggests that cultures, hierarchies, and leadership may well be as important as other more concrete or tangible tools,[7] but these have seldom been evaluated as part of studies on improving the response to deterioration. The pediatric early warning system utilization and mortality avoidance (PUMA) study, a research program funded by the National Institute for Health Research (United Kingdom), is exploring these tools and will likely report later in 2019.[8]

Two immediate practical implications of this work emerge, which should be of relevance to clinical leaders in children's hospitals. The first is that it is highly likely that there will be some events you cannot anticipate. A bronchiolitic infant is always likely to suddenly plug off, and invasive group A streptococcus is a mastery of mimicry and deceit. The authors noted that even with a mature, long-standing Rapid Response System process, ETs were still associated with adverse outcomes. Therefore, it may well be that the ET metric measured over time delineates a locally defined acceptable level of unplanned intensive care admission. If your hospital is significantly above this, they must seriously look at how they can improve their performance. It should be noted here that there were only 45 ETs identified in 4.5 years in Cincinnati and 50% of these were from specialist units within the hospital. It is possible that perhaps the ETs will in the future become as rare as mortality is today, and as hospitals improve, new frames of reference will be needed.

These new references are likely to come from high-performing child health institutions such as those in Philadelphia and Cincinnati, and this leads to a second important principle that hospitals should acknowledge. One of the reasons for patient safety success is the relentless pursuit of excellence. The very act of consistently, and transparently, auditing and analyzing performance is vital to change outcomes. We should digest, evaluate, adopt, and improve the research that groups such as these are undertaking as, although sometimes imperfect, they should also inspire us to ensure that children in our own institutions are as safe as they possibly can be.

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Interhospital Transfers for Quality Assessment of Healthcare Systems

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With the increasing percentage of our gross national product being allotted to healthcare and concerns about the care received by patients, the number of measures to assess the quality and efficiency of care delivered by healthcare professionals has increased. The paper by Mueller et al.[1] adds to our understanding of an important yet relatively understudied group of patients: those that require transfer from one inpatient facility to another. In general, these patients are sicker and exhibit poor outcomes, especially with time-sensitive management conditions, such as cerebrovascular accidents, or conditions where the transfer itself may cause harm to the patient, such as the case of an infant born prematurely. However, transferring patients with less time-dependent conditions may not be associated with such negative results.[1] The uniqueness of interhospital transfers is attributed to their ability to provide insights into the care practices of other actors within the healthcare system, namely, the transferring hospital and the larger healthcare system, and to describe how the care quality may change in hospitals during periods of stress, such as during overcrowding or high patient acuity.

As described by Mueller et al. the care and outcomes of patients transferred to a hospital may provide information regarding the key aspects of care at the receiving hospital; these aspects include the capability for triage of potentially high-acuity patients and the management of such patients during periods of crowding and organizational stress. These measures of efficiency have rarely been studied in relation to the care provided to patients and their ultimate outcomes. The most studied efficiency measure is hospital crowding, which has been shown in numerous studies to be associated with lower efficiency as measured by the length of stay, lower quality of care, and higher mortality.[2-3] This report by Mueller et al. is one of the first papers to highlight how other aspects of the care delivery system, including the triage practices and the response of a hospital system to stress, may influence care outcomes. The limitation of other studies in exploring the relationship between the measures of efficiency and quality of care, as noted by a systematic review of healthcare efficiency measures by Hussey et al.[4] emphasizes the need to understand the drivers of low quality of care and to determine the specific times at which such care may be compromised by other factors, such as patient volumes.

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Although interhospital transfers may offer certain insights into the efficiency of care delivered at the hospitals receiving these patients, they are generally rare and centered on a few quaternary hospitals within a region.[3] In addition, the Mueller paper reveals that not all these transfers have high disease acuity, particularly for cardiac patients. Whether claims-based approaches to risk adjustment would sufficiently differentiate the reasons for the transfer/failure to transfer of patients is unclear and thus may be affected by the selection bias. With these issues, the outcome of transferred patients may be only of limited value when assessing the care quality of hospitals that generally receive transferred patients from other medical institutions within a given geographic area.[5]

Interhospital transfers may provide insights into the care of patients at the hospitals which transfer out such patients, focusing on the appropriateness of transfers, how these hospitals operate when such a sick patient arrives at that hospital, and the outcomes of patients with conditions that may require transfer. A few studies have explored the preventable transfer, particularly for trauma patients, where a preventable transfer was defined as a transfer that was was not admitted to the receiving hospital and did not receive any procedures or testing. Although not readily defined for numerous conditions, such a measure would provide insights into how hospitals decide whether a patient requires care at a higher-level hospital and assessing the processes needed to optimize this decision-making process, including where the patient ultimately is transferred. In a study of patients with acute myocardial infarction, 36.8% of cases that required transfer were not directed to hospitals with the best outcomes as measured by 30-day risk-adjusted mortality rates within a given geographic region.[6] Such decisions would contribute to the potential worse outcomes observed in patients requiring interhospital transfer.

Finally, transfers provide insights into the functioning of the larger healthcare system. The measures assessing the functioning of the healthcare system are rare. In theory, interhospital transfers meet the goals of a functioning regional healthcare system by matching the patients to facilities with the suitable capabilities to manage the patient's given type of illness or injury. Such a system, however, requires collaboration between hospitals who otherwise compete for patients. The literature suggests that such collaboration is widely variable and dependent on patient factors, such as the types of conditions and their insurance status,[7] and the costs required by hospitals to add the services needed to care for increasingly ill patients. In addition, the growth of so-called narrow insurance networks, which limit the number of hospitals an insurance company will

include on their preferred network, may place barriers on the appropriate location of such transfers based on the quality of the receiving hospital.[8]

The paper by Mueller et al. adds to the literature the unique aspects of the care needed by the patients requiring interhospital transfer. Unlike most other measures of care quality and efficiency, interhospital transfers potentially offer knowledge about the quality of the larger healthcare system, assessing the appropriateness and ultimate outcomes not only of patients who are transferred but similarly sick patients who could have potentially benefited from a transfer and how the actors within the system may respond to periods of high patient load and stress. By understanding the drivers of the appropriateness of where patients receive care, we can gain insights into the mechanisms needed to fulfill the goals of a functional regionalized healthcare system.

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Not Salty Enough

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We commend Gottenborg and Pierce on their well-written summary of the 2013 National Institutes of Care Excellence (NICE) guidelines on intravenous fluids (IV) for adults.[1] One area of the guidelines that we believe should be modified is the outdated recommendation for prescribing 1 mmol/kg/day of sodium.[2] At the guideline recommended rate of 25-30 mL/kg/day, a 75 kg adult would be prescribed a solution of 25-30 mmol/L of sodium or 0.18% saline, which is in stark contrast to the more recent recommendations of isotonic fluids from the 2018 American Academy of Pediatrics and 2015 NICE pediatric guidelines.[3,4] 0.18% saline is extremely hypotonic compared to plasma sodium and would place hospitalized patients at significant risk for developing hospital-acquired hyponatremia.

The recommendations for hypotonic solutions were largely developed from theoretical research in the 1950s before the first description of the syndrome of inappropriate secretion of antidiuretic hormone.[5] Hospitalized patients are at significant risk for nonosmotic stimuli for antidiuretic hormone secretion, and hypotonic fluids increase the risk of hyponatremia, which can have catastrophic complications. We believe the pediatric evidence should be extrapolated and included with the supporting (albeit limited) adult evidence, and that when indicated, isotonic fluids should be the maintenance fluid for most hospitalized adults.[3-4,6]

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