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Dr. Christopher Sankey, hospitalist and associate program director of the traditional internal medicine residency Program at Yale School of Medicine.

Courtesy Yale School of Medicine/Anthony DeCarlo

COVID redefines curriculum for hospitalists-in-training

Pandemic brings 'clarity and urgency'

By Larry Beresford

The coronavirus pandemic has impacted all facets of the education and training of this country's future hospitalists, including their medical school coursework, elective rotations, clerkships, and residency training – although with variations between settings and localities.

The COVID-19 crisis demanded immediate changes in traditional approaches to medical education. Training programs responded quickly to institute those changes. As hospitals geared up for potential surges in COVID cases starting in mid-March, many onsite training activities for medical students were shut down in order to reserve personal protective equipment for essential personnel and not put learners at risk of catching the virus. A variety of events related to their education were canceled. Didactic presentations and meetings were converted to virtual gatherings on internet platforms such

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Medicare fines half of hospitals for readmitting too many patients

By Jordan Rau
Kaiser Health News

Nearly half the nation's hospitals, many of which are still wrestling with the financial fallout of the unexpected coronavirus, will get lower payments for all Medicare patients because of their history of readmitting patients, federal records show.

The penalties are the ninth annual round of the Hospital Readmissions Reduction Program created as part of the Affordable Care Act's broader effort to improve quality and lower

PRADIT_PH/THINKSTOCK

costs. The latest penalties are calculated using each hospital case history between July 2016 and June 2019, so the flood of coronavirus patients that have swamped hospitals this year were not included.

The Centers for Medicare & Medicaid Services announced in September it may suspend the penalty program in the future if the chaos surrounding the pandemic, including the spring's moratorium on elective surgeries, makes it too difficult to assess hospital performance.

For this year, the penalties remain in effect. Retroactive to the federal fiscal year that began Oct. 1, Medicare will lower a year's worth of payments to 2,545 hospitals, the data show. The average reduction is 0.69%, with 613 hospitals receiving a penalty of 1% or more.

Out of 5,267 hospitals in the country, Congress has exempted 2,176 from the threat of penalties, either because they are critical access hospitals – defined as the only inpatient facility in an area – or hospitals that specialize in psychiatric patients, children, veterans, rehabilitation, or long-term care. Of the 3,080 hospitals CMS evaluated, 83% received a penalty.

The number and severity of penalties were comparable to those of recent years, although the number of hospitals receiving the maximum penalty of 3% dropped from 56 to 39. Because the penalties are applied to new admission payments, the total dollar amount each hospital will lose will not be known until after the fiscal year ends on July 30.

"It's unfortunate that hospitals will face readmission penalties in fiscal year 2021," said Akin Demehin, director of policy at the American Hospital Association. "Given the financial strain that hospitals are under, every dollar counts, and the impact of any penalty is significant."

The penalties are based on readmissions of Medicare patients who initially came to the hospital with diagnoses of congestive heart failure, heart attack, pneumonia, chronic obstructive pulmonary disease, hip or knee replacement, or coronary artery bypass graft surgery. Medicare counts as a readmission any of those patients who ended up back in any hospital within 30 days of discharge, except for planned returns like a second phase of surgery.

A hospital will be penalized if its readmission rate is higher than expected given the national trends in any one of those categories.

The industry has disapproved of the program since its inception, complaining that the measures are not precise and it unfairly punishes hospitals that treat low-income patients.

Michael Millenson, a health quality consultant who focuses on patient safety, said the penalties are a useful but imperfect mechanism to push hospitals to improve their care. The designers of the penalty system envisioned it as a way to neutralize the economic benefit hospitals get from readmitted patients under Medicare's fee-for-service payment model, as they are otherwise paid for two stays instead of just one.

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Eliquis® (apixaban) tablets 5mg 2.5mg

*BASED ON CLINICAL TRIAL DATA VS ENOXAPARIN/WARFARIN IN PATIENTS WITH DVT/PE.

Visit EliquisData.com

INDICATION

ELIQUIS is indicated for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and to reduce the risk of recurrent DVT and PE following initial therapy.

SELECTED IMPORTANT SAFETY INFORMATION

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

(A) Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.

(B) Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated.

CONTRAINDICATIONS

- Active pathological bleeding
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions)

Please see additional Important Safety Information and accompanying Brief Summary of Full Prescribing Information, including **Boxed WARNINGS,** on the adjacent pages.

AMPLIFY study design[1,2]

A randomized, double-blind, phase III trial to determine whether ELIQUIS was noninferior to enoxaparin/warfarin for the incidence of recurrent venous thromboembolism (VTE)* or VTE-related death in 5400 patients with objectively confirmed, symptomatic proximal deep vein thrombosis (DVT)/pulmonary embolism (PE). 2693 patients were randomized to ELIQUIS 10 mg orally twice daily for 7 days followed by 5 mg orally twice daily for 6 months, and 2707 patients were randomized to standard of care, which was initial enoxaparin 1 mg/kg twice daily subcutaneously for at least 5 days (until INR ≥2), followed by warfarin (target INR range: 2.0-3.0) orally for 6 months. The primary efficacy endpoint was recurrent VTE* or VTE-related death, and the primary safety endpoint was major bleeding.

≈90% of patients in the AMPLIFY trial had an unprovoked DVT/PE at baseline.[1]

- The 10% of patients with a provoked DVT/PE were required to have an additional ongoing risk factor in order to be randomized†

*Recurrent symptomatic VTE (nonfatal DVT or nonfatal PE).
†Risk factors included previous episode of DVT/PE, immobilization, history of cancer, active cancer, and known prothrombotic genotype.

SELECTED IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

- **Increased Risk of Thrombotic Events after Premature Discontinuation:** Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
- **Bleeding Risk:** ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.
  - Concomitant use of drugs affecting hemostasis increases the risk of bleeding, including aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, SSRIs, SNRIs, and NSAIDs.
  - Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.
  - The anticoagulant effect of apixaban can be expected to persist for at least 24 hours after the last dose (i.e., about two half-lives). An agent to reverse the anti-factor Xa activity of apixaban is available. Please visit www.andexxa.com for more information on availability of a reversal agent.
- **Spinal/Epidural Anesthesia or Puncture:** Patients treated with ELIQUIS undergoing spinal/epidural anesthesia or puncture may develop an epidural or spinal hematoma which can result in long-term or permanent paralysis.

  The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

  Monitor patients frequently and if neurological compromise is noted, urgent diagnosis and treatment is necessary. Physicians should consider the potential benefit versus the risk of neuraxial intervention in ELIQUIS patients.
- **Prosthetic Heart Valves:** The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves and is not recommended in these patients.
- **Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy:** Initiation of ELIQUIS is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.
- **Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome (APS):** Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive APS. For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

ADVERSE REACTIONS

- The most common and most serious adverse reactions reported with ELIQUIS were related to bleeding.

TEMPORARY INTERRUPTION FOR SURGERY AND OTHER INTERVENTIONS

- ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be noncritical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established.

DRUG INTERACTIONS

- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, or ritonavir). In patients already taking 2.5 mg twice daily, avoid coadministration of ELIQUIS with combined P-gp and strong CYP3A4 inhibitors.

  Clarithromycin
  Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS.

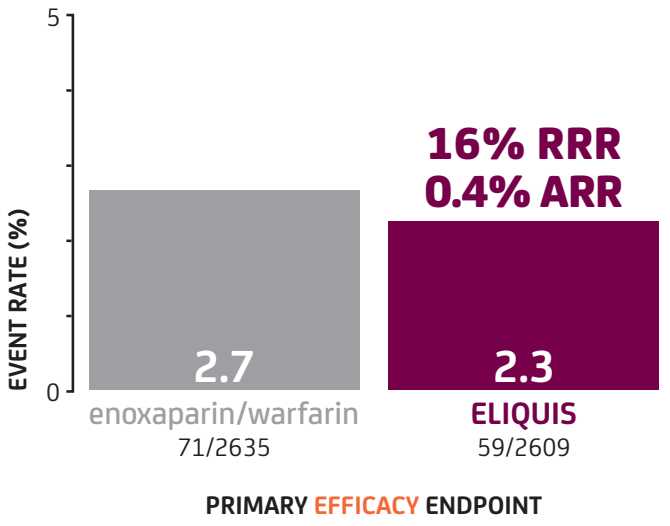
FOR THE TREATMENT OF DVT/PE

ONLY ELIQUIS demonstrated BOTH comparable efficacy AND superiority in major bleeding events vs enoxaparin/warfarin[1]

COMPARABLE

in VTE*/VTE-related death

RR=0.84 (95% CI: 0.60–1.18); *P*<0.0001 for noninferiority

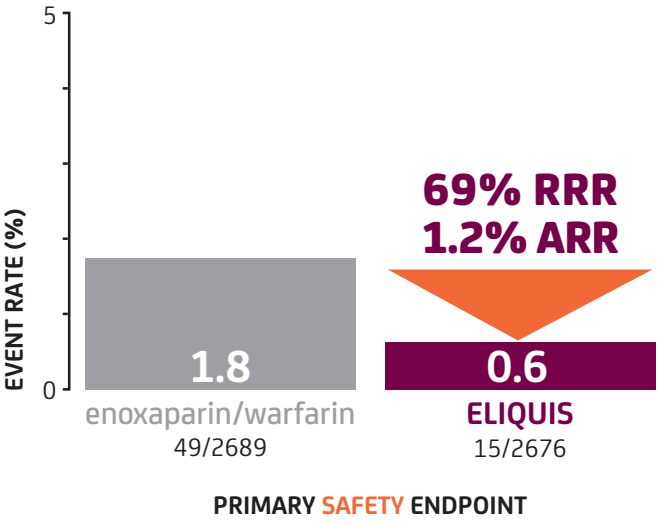


PRIMARY EFFICACY ENDPOINT

SUPERIOR

Major bleeding‡

RR=0.31 (95% CI: 0.17–0.55); *P*<0.0001



PRIMARY SAFETY ENDPOINT

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding.[1]

- Discontinuation rate due to bleeding events: 0.7% in ELIQUIS-treated patients vs 1.7% with enoxaparin/warfarin[1]
- In AMPLIFY, the most commonly observed adverse reactions in ELIQUIS-treated patients (incidence ≥1%) were epistaxis, contusion, hematuria, menorrhagia, hematoma, hemoptysis, rectal hemorrhage, and gingival bleeding[1]

Major bleeding was defined as clinically overt bleeding accompanied by ≥1 of the following[2,3]:

A decrease in hemoglobin of ≥2 g/dL over 24 hours; transfusion of 2 or more units of packed red blood cells; bleeding that occurred in at least one of the following critical sites: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; and fatal bleeding.

‡Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.
ARR=absolute risk reduction; CI=confidence interval; INR=international normalized ratio; RR=relative risk; RRR=relative risk reduction.

SELECTED IMPORTANT SAFETY INFORMATION

DRUG INTERACTIONS (cont'd)

- **Combined P-gp and Strong CYP3A4 Inducers:** Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban.
- **Anticoagulants and Antiplatelet Agents:** Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding. APPRAISE-2, a placebo-controlled clinical trial of apixaban in high-risk post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with apixaban compared to placebo.

PREGNANCY

- The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery, and in the fetus and neonate.
  - *Labor or delivery*: ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches.

LACTATION

- Breastfeeding is not recommended during treatment with ELIQUIS.

References: 1. Eliquis [package insert]. Bristol-Myers Squibb Company, Princeton, NJ, and Pfizer Inc, New York, NY. **2.** Agnelli G, Buller HR, Cohen A, et al; for AMPLIFY Investigators. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808. Supplement available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1302507/suppl_file/nejmoa1302507_appendix.pdf. Accessed April 14, 2020. **3.** Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. *N Engl J Med.* 2013;368(8):699-708. Supplement available at http://www.nejm.org/doi/suppl/10.1056/NEJMoa1207541/suppl_file/nejmoa1207541_appendix.pdf. Accessed April 14, 2020.

Please see accompanying Brief Summary of Full Prescribing Information, including **Boxed WARNINGS,** on the adjacent pages.

Eliquis® (apixaban) tablets 5mg 2.5mg

Bristol Myers Squibb™ Pfizer

ELIQUIS® (apixaban) tablets, for oral use

℞ ONLY

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

WARNING: (A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

(B) SPINAL/EPIDURAL HEMATOMA

(A) PREMATURE DISCONTINUATION OF ELIQUIS INCREASES THE RISK OF THROMBOTIC EVENTS

Premature discontinuation of any oral anticoagulant, including ELIQUIS, increases the risk of thrombotic events. If anticoagulation with ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration, Warnings and Precautions, and Clinical Studies (14.1) in full Prescribing Information]*.

(B) SPINAL/EPIDURAL HEMATOMA

Epidural or spinal hematomas may occur in patients treated with ELIQUIS who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures. Factors that can increase the risk of developing epidural or spinal hematomas in these patients include:

- **use of indwelling epidural catheters**
- **concomitant use of other drugs that affect hemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants**
- **a history of traumatic or repeated epidural or spinal punctures**
- **a history of spinal deformity or spinal surgery**
- **optimal timing between the administration of ELIQUIS and neuraxial procedures is not known**

[see Warnings and Precautions]

Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Warnings and Precautions]*.

Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated *[see Warnings and Precautions]*.

INDICATIONS AND USAGE

Reduction of Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation— ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery— ELIQUIS is indicated for the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients who have undergone hip or knee replacement surgery.

Treatment of Deep Vein Thrombosis—ELIQUIS is indicated for the treatment of DVT.

Treatment of Pulmonary Embolism—ELIQUIS is indicated for the treatment of PE.

Reduction in the Risk of Recurrence of DVT and PE—ELIQUIS is indicated to reduce the risk of recurrent DVT and PE following initial therapy.

DOSAGE AND ADMINISTRATION (Selected information)

Temporary Interruption for Surgery and Other Interventions

ELIQUIS should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding *[see Warnings and Precautions]*. ELIQUIS should be discontinued at least 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled. Bridging anticoagulation during the 24 to 48 hours after stopping ELIQUIS and prior to the intervention is not generally required. ELIQUIS should be restarted after the surgical or other procedures as soon as adequate hemostasis has been established. (For complete *Dosage and Administration* section, see full Prescribing Information.)

CONTRAINDICATIONS

ELIQUIS is contraindicated in patients with the following conditions:

- Active pathological bleeding *[see Warnings and Precautions and Adverse Reactions]*
- Severe hypersensitivity reaction to ELIQUIS (e.g., anaphylactic reactions) *[see Adverse Reactions]*

WARNINGS AND PRECAUTIONS

Increased Risk of Thrombotic Events after Premature Discontinuation

Premature discontinuation of any oral anticoagulant, including ELIQUIS, in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from ELIQUIS to warfarin in clinical trials in atrial fibrillation patients. If ELIQUIS is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant *[see Dosage and Administration (2.4) and Clinical Studies (14.1) in full Prescribing Information]*.

Bleeding

ELIQUIS increases the risk of bleeding and can cause serious, potentially fatal, bleeding *[see Dosage and Administration (2.1) in full Prescribing Information and Adverse Reactions]*.

Concomitant use of drugs affecting hemostasis increases the risk of bleeding. These include aspirin and other antiplatelet agents, other anticoagulants, heparin, thrombolytic agents, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, and nonsteroidal anti-inflammatory drugs (NSAIDs) *[see Drug Interactions]*.

Advise patients of signs and symptoms of blood loss and to report them immediately or go to an emergency room. Discontinue ELIQUIS in patients with active pathological hemorrhage.

Reversal of Anticoagulant Effect

An agent to reverse the anti-factor Xa activity of apixaban is available. The pharmacodynamic effect of ELIQUIS can be expected to persist for at least 24 hours after the last dose, i.e., for about two drug half-lives. Prothrombin complex concentrate (PCC), activated prothrombin complex concentrate or recombinant factor VIIa may be considered, but have not been evaluated in clinical studies *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. When PCCs are used, monitoring for the anticoagulation effect of apixaban using a clotting test (PT, INR, or aPTT) or anti-factor Xa (FXa) activity is not useful and is not recommended. Activated oral charcoal reduces absorption of apixaban, thereby lowering apixaban plasma concentration *[see Overdosage]*.

Hemodialysis does not appear to have a substantial impact on apixaban exposure *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of apixaban. There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving apixaban. There is no experience with systemic hemostatics (desmopressin) in individuals receiving ELIQUIS, and they are not expected to be effective as a reversal agent.

Spinal/Epidural Anesthesia or Puncture

When neuraxial anesthesia (spinal/epidural anesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events may be increased by the postoperative use of indwelling epidural catheters or the concomitant use of medicinal products affecting hemostasis. Indwelling epidural or intrathecal catheters should not be removed earlier than 24 hours after the last administration of ELIQUIS. The next dose of ELIQUIS should not be administered earlier than 5 hours after the removal of the catheter. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, delay the administration of ELIQUIS for 48 hours.

Monitor patients frequently for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, or bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

Patients with Prosthetic Heart Valves

The safety and efficacy of ELIQUIS have not been studied in patients with prosthetic heart valves. Therefore, use of ELIQUIS is not recommended in these patients.

Acute PE in Hemodynamically Unstable Patients or Patients who Require Thrombolysis or Pulmonary Embolectomy

Initiation of ELIQUIS (apixaban) is not recommended as an alternative to unfractionated heparin for the initial treatment of patients with PE who present with hemodynamic instability or who may receive thrombolysis or pulmonary embolectomy.

Increased Risk of Thrombosis in Patients with Triple Positive Antiphospholipid Syndrome

Direct-acting oral anticoagulants (DOACs), including ELIQUIS, are not recommended for use in patients with triple-positive antiphospholipid syndrome (APS). For patients with APS (especially those who are triple positive [positive for lupus anticoagulant, anticardiolipin, and anti–beta 2-glycoprotein I antibodies]), treatment with DOACs has been associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the prescribing information.

- Increased Risk of Thrombotic Events After Premature Discontinuation *[see Warnings and Precautions]*
- Bleeding *[see Warnings and Precautions]*
- Spinal/Epidural Anesthesia or Puncture *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The safety of ELIQUIS was evaluated in the ARISTOTLE and AVERROES studies *[see Clinical Studies (14) in full Prescribing Information]*, including 11,284 patients exposed to ELIQUIS 5 mg twice daily and 602 patients exposed to ELIQUIS 2.5 mg twice daily. The duration of ELIQUIS exposure was ≥12 months for 9375 patients and ≥24 months for 3369 patients in the two studies. In ARISTOTLE, the mean duration of exposure was 89 weeks (>15,000 patient-years). In AVERROES, the mean duration of exposure was approximately 59 weeks (>3000 patient-years).

The most common reason for treatment discontinuation in both studies was for bleeding-related adverse reactions; in ARISTOTLE this occurred in 1.7% and 2.5% of patients treated with ELIQUIS and warfarin, respectively, and in AVERROES, in 1.5% and 1.3% on ELIQUIS and aspirin, respectively.

Bleeding in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE and AVERROES

Tables 1 and 2 show the number of patients experiencing major bleeding during the treatment period and the bleeding rate (percentage of subjects with at least one bleeding event per 100 patient-years) in ARISTOTLE and AVERROES.

Table 1: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in ARISTOTLE*

	ELIQUIS N=9088 n (per 100 pt-year)	Warfarin N=9052 n (per 100 pt-year)	Hazard Ratio (95% CI)	P-value
Major†	327 (2.13)	462 (3.09)	0.69 (0.60, 0.80)	<0.0001
Intracranial (ICH)‡	52 (0.33)	125 (0.82)	0.41 (0.30, 0.57)	-
Hemorrhagic stroke§	38 (0.24)	74 (0.49)	0.51 (0.34, 0.75)	-
Other ICH	15 (0.10)	51 (0.34)	0.29 (0.16, 0.51)	-
Gastrointestinal (GI)¶	128 (0.83)	141 (0.93)	0.89 (0.70, 1.14)	-
Fatal**	10 (0.06)	37 (0.24)	0.27 (0.13, 0.53)	-
Intracranial	4 (0.03)	30 (0.20)	0.13 (0.05, 0.37)	-
Non-intracranial	6 (0.04)	7 (0.05)	0.84 (0.28, 2.15)	-

* Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints. Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period).

† Defined as clinically overt bleeding accompanied by one or more of the following: a decrease in hemoglobin of ≥2 g/dL, a transfusion of 2 or more units of packed red blood cells, bleeding at a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal or with fatal outcome.

‡ Intracranial bleed includes intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as an intracranial major bleed.

§ On-treatment analysis based on the safety population, compared to ITT analysis presented in Section 14 in the full Prescribing Information.

¶ GI bleed includes upper GI, lower GI, and rectal bleeding.

** Fatal bleeding is an adjudicated death with the primary cause of death as intracranial bleeding or non-intracranial bleeding during the on-treatment period.

In ARISTOTLE, the results for major bleeding were generally consistent across most major subgroups including age, weight, $CHADS_2$ score (a scale from 0 to 6 used to estimate risk of stroke, with higher scores predicting greater risk), prior warfarin use, geographic region, and aspirin use at randomization (Figure 1). Subjects treated with ELIQUIS with diabetes bled more (3% per year) than did subjects without diabetes (1.9% per year).

Table 2: Bleeding Events in Patients with Nonvalvular Atrial Fibrillation in AVERROES

	ELIQUIS (apixaban) N=2798 n (%/year)	Aspirin N=2780 n (%/year)	Hazard Ratio (95% CI)	P-value
Major	45 (1.41)	29 (0.92)	1.54 (0.96, 2.45)	0.07
Fatal	5 (0.16)	5 (0.16)	0.99 (0.23, 4.29)	-
Intracranial	11 (0.34)	11 (0.35)	0.99 (0.39, 2.51)	-

Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Other Adverse Reactions

Hypersensitivity reactions (including drug hypersensitivity, such as skin rash, and anaphylactic reactions, such as allergic edema) and syncope were reported in <1% of patients receiving ELIQUIS.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery

The safety of ELIQUIS has been evaluated in 1 Phase II and 3 Phase III studies including 5924 patients exposed to ELIQUIS 2.5 mg twice daily undergoing major orthopedic surgery of the lower limbs (elective hip replacement or elective knee replacement) treated for up to 38 days.

In total, 11% of the patients treated with ELIQUIS 2.5 mg twice daily experienced adverse reactions.

Bleeding results during the treatment period in the Phase III studies are shown in Table 3. Bleeding was assessed in each study beginning with the first dose of double-blind study drug.

Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

Bleeding Endpoint*	ADVANCE-3 Hip Replacement Surgery		ADVANCE-2 Knee Replacement Surgery		ADVANCE-1 Knee Replacement Surgery	
	ELIQUIS 2.5 mg po bid 35±3 days	Enoxaparin 40 mg sc qd 35±3 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 40 mg sc qd 12±2 days	ELIQUIS 2.5 mg po bid 12±2 days	Enoxaparin 30 mg sc q12h 12±2 days
	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 9 to 15 hours prior to surgery	First dose 12 to 24 hours post surgery	First dose 12 to 24 hours post surgery
All treated	N=2673	N=2659	N=1501	N=1508	N=1596	N=1588
Major (including surgical site)	22 (0.82%)†	18 (0.68%)	9 (0.60%)‡	14 (0.93%)	11 (0.69%)	22 (1.39%)
Fatal	0	0	0	0	0	1 (0.06%)
Hgb decrease ≥2 g/dL	13 (0.49%)	10 (0.38%)	8 (0.53%)	9 (0.60%)	10 (0.63%)	16 (1.01%)
Transfusion of ≥2 units RBC	16 (0.60%)	14 (0.53%)	5 (0.33%)	9 (0.60%)	9 (0.56%)	18 (1.13%)
Bleed at critical site§	1 (0.04%)	1 (0.04%)	1 (0.07%)	2 (0.13%)	1 (0.06%)	4 (0.25%)
Major + CRNM¶	129 (4.83%)	134 (5.04%)	53 (3.53%)	72 (4.77%)	46 (2.88%)	68 (4.28%)
All	313 (11.71%)	334 (12.56%)	104 (6.93%)	126 (8.36%)	85 (5.33%)	108 (6.80%)

* All bleeding criteria included surgical site bleeding.

† Includes 13 subjects with major bleeding events that occurred before the first dose of ELIQUIS (administered 12 to 24 hours post-surgery).

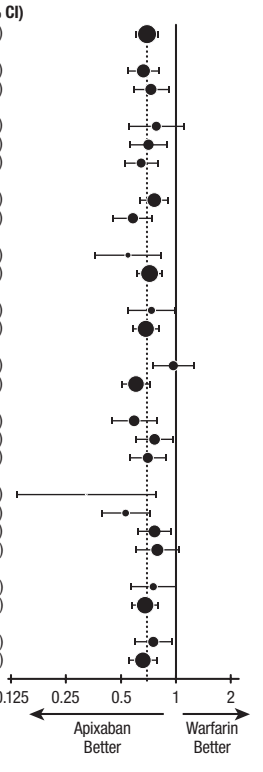
‡ Includes 5 subjects with major bleeding events that occurred before the first dose of ELIQUIS (administered 12 to 24 hours post-surgery).

§ Intracranial, intraspinal, intraocular, pericardial, an operated joint requiring re-operation or intervention, intramuscular with compartment syndrome, or retroperitoneal. Bleeding into an operated joint requiring re-operation or intervention was present in all patients with this category of bleeding. Events and event rates include one enoxaparin-treated patient in ADVANCE-1 who also had intracranial hemorrhage.

¶ CRNM = clinically relevant nonmajor.

Figure 1: Major Bleeding Hazard Ratios by Baseline Characteristics – ARISTOTLE Study

Subgroup	n of Events / N of Patients (% per year) Apixaban	Warfarin	Hazard Ratio (95% CI)
All Patients	327 / 9088 (2.1)	462 / 9052 (3.1)	0.69 (0.60, 0.80)
Prior Warfarin/VKA Status			
Experienced (57%)	185 / 5196 (2.1)	274 / 5180 (3.2)	0.66 (0.55, 0.80)
Naive (43%)	142 / 3892 (2.2)	188 / 3872 (3.0)	0.73 (0.59, 0.91)
Age			
<65 (30%)	56 / 2723 (1.2)	72 / 2732 (1.5)	0.78 (0.55, 1.11)
≥65 and <75 (39%)	120 / 3529 (2.0)	166 / 3501 (2.8)	0.71 (0.56, 0.89)
≥75 (31%)	151 / 2836 (3.3)	224 / 2819 (5.2)	0.64 (0.52, 0.79)
Sex			
Male (65%)	225 / 5868 (2.3)	294 / 5879 (3.0)	0.76 (0.64, 0.90)
Female (35%)	102 / 3220 (1.9)	168 / 3173 (3.3)	0.58 (0.45, 0.74)
Weight			
≤60 kg (11%)	36 / 1013 (2.3)	62 / 965 (4.3)	0.55 (0.36, 0.83)
>60 kg (89%)	290 / 8043 (2.1)	398 / 8059 (3.0)	0.72 (0.62, 0.83)
Prior Stroke or TIA			
Yes (19%)	77 / 1687 (2.8)	106 / 1735 (3.9)	0.73 (0.54, 0.98)
No (81%)	250 / 7401 (2.0)	356 / 7317 (2.9)	0.68 (0.58, 0.80)
Diabetes Mellitus			
Yes (25%)	112 / 2276 (3.0)	114 / 2250 (3.1)	0.96 (0.74, 1.25)
No (75%)	215 / 6812 (1.9)	348 / 6802 (3.1)	0.60 (0.51, 0.71)
$CHADS_2$ Score			
≤1 (34%)	76 / 3093 (1.4)	126 / 3076 (2.3)	0.59 (0.44, 0.78)
2 (36%)	125 / 3246 (2.3)	163 / 3246 (3.0)	0.76 (0.60, 0.96)
≥3 (30%)	126 / 2749 (2.9)	173 / 2730 (4.1)	0.70 (0.56, 0.88)
Creatinine Clearance			
<30 mL/min (1%)	7 / 136 (3.7)	19 / 132 (11.9)	0.32 (0.13, 0.78)
30-50 mL/min (15%)	66 / 1357 (3.2)	123 / 1380 (6.0)	0.53 (0.39, 0.71)
>50-80 mL/min (42%)	157 / 3807 (2.5)	199 / 3758 (3.2)	0.76 (0.62, 0.94)
>80 mL/min (41%)	96 / 3750 (1.5)	119 / 3746 (1.8)	0.79 (0.61, 1.04)
Geographic Region			
US (19%)	83 / 1716 (2.8)	109 / 1693 (3.8)	0.75 (0.56, 1.00)
Non-US (81%)	244 / 7372 (2.0)	353 / 7359 (2.9)	0.68 (0.57, 0.80)
Aspirin at Randomization			
Yes (31%)	129 / 2846 (2.7)	164 / 2762 (3.7)	0.75 (0.60, 0.95)
No (69%)	198 / 6242 (1.9)	298 / 6290 (2.8)	0.66 (0.55, 0.79)



Note: The figure above presents effects in various subgroups, all of which are baseline characteristics and all of which were prespecified, if not the groupings. The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Adverse reactions occurring in ≥1% of patients undergoing hip or knee replacement surgery in the 1 Phase II study and the 3 Phase III studies are listed in Table 4.

Table 4: Adverse Reactions Occurring in ≥1% of Patients in Either Group Undergoing Hip or Knee Replacement Surgery

	ELIQUIS (apixaban), n (%) 2.5 mg po bid N=5924	Enoxaparin, n (%) 40 mg sc qd or 30 mg sc q12h N=5904
Nausea	153 (2.6)	159 (2.7)
Anemia (including postoperative and hemorrhagic anemia, and respective laboratory parameters)	153 (2.6)	178 (3.0)
Contusion	83 (1.4)	115 (1.9)
Hemorrhage (including hematoma, and vaginal and urethral hemorrhage)	67 (1.1)	81 (1.4)
Postprocedural hemorrhage (including postprocedural hematoma, wound hemorrhage, vessel puncture-site hematoma and catheter-site hemorrhage)	54 (0.9)	60 (1.0)
Transaminases increased (including alanine aminotransferase increased and alanine aminotransferase abnormal)	50 (0.8)	71 (1.2)
Aspartate aminotransferase increased	47 (0.8)	69 (1.2)
Gamma-glutamyltransferase increased	38 (0.6)	65 (1.1)

Less common adverse reactions in ELIQUIS-treated patients undergoing hip or knee replacement surgery occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: thrombocytopenia (including platelet count decreases)

Vascular disorders: hypotension (including procedural hypotension)

Respiratory, thoracic, and mediastinal disorders: epistaxis

Gastrointestinal disorders: gastrointestinal hemorrhage (including hematemesis and melena), hematochezia

Hepatobiliary disorders: liver function test abnormal, blood alkaline phosphatase increased, blood bilirubin increased

Renal and urinary disorders: hematuria (including respective laboratory parameters)

Injury, poisoning, and procedural complications: wound secretion, incision-site hemorrhage (including incision-site hematoma), operative hemorrhage

Less common adverse reactions in ELIQUIS-treated patients undergoing hip or knee replacement surgery occurring at a frequency of <0.1%:

Gingival bleeding, hemoptysis, hypersensitivity, muscle hemorrhage, ocular hemorrhage (including conjunctival hemorrhage), rectal hemorrhage

Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT or PE

The safety of ELIQUIS has been evaluated in the AMPLIFY and AMPLIFY-EXT studies, including 2676 patients exposed to ELIQUIS 10 mg twice daily, 3359 patients exposed to ELIQUIS 5 mg twice daily, and 840 patients exposed to ELIQUIS 2.5 mg twice daily.

Common adverse reactions (≥1%) were gingival bleeding, epistaxis, contusion, hematuria, rectal hemorrhage, hematoma, menorrhagia, and hemoptysis.

AMPLIFY Study

The mean duration of exposure to ELIQUIS was 154 days and to enoxaparin/warfarin was 152 days in the AMPLIFY study. Adverse reactions related to bleeding occurred in 417 (15.6%) ELIQUIS-treated patients compared to 661 (24.6%) enoxaparin/warfarin-treated patients. The discontinuation rate due to bleeding events was 0.7% in the ELIQUIS-treated patients compared to 1.7% in enoxaparin/warfarin-treated patients in the AMPLIFY study.

In the AMPLIFY study, ELIQUIS was statistically superior to enoxaparin/warfarin in the primary safety endpoint of major bleeding (relative risk 0.31, 95% CI [0.17, 0.55], P-value <0.0001).

Bleeding results from the AMPLIFY study are summarized in Table 5.

Table 5: Bleeding Results in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)	Relative Risk (95% CI)
Major	15 (0.6)	49 (1.8)	0.31 (0.17, 0.55) p<0.0001
CRNM*	103 (3.9)	215 (8.0)	
Major + CRNM	115 (4.3)	261 (9.7)	
Minor	313 (11.7)	505 (18.8)	
All	402 (15.0)	676 (25.1)	

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY study are listed in Table 6.

Table 6: Adverse Reactions Occurring in ≥1% of Patients Treated for DVT and PE in the AMPLIFY Study

	ELIQUIS N=2676 n (%)	Enoxaparin/Warfarin N=2689 n (%)
Epistaxis	77 (2.9)	146 (5.4)
Contusion	49 (1.8)	97 (3.6)
Hematuria	46 (1.7)	102 (3.8)
Menorrhagia	38 (1.4)	30 (1.1)
Hematoma	35 (1.3)	76 (2.8)
Hemoptysis	32 (1.2)	31 (1.2)
Rectal hemorrhage	26 (1.0)	39 (1.5)
Gingival bleeding	26 (1.0)	50 (1.9)

AMPLIFY-EXT Study

The mean duration of exposure to ELIQUIS was approximately 330 days and to placebo was 312 days in the AMPLIFY-EXT study. Adverse reactions related to bleeding occurred in 219 (13.3%) ELIQUIS-treated patients compared to 72 (8.7%) placebo-treated patients. The discontinuation rate due to bleeding events was approximately 1% in the ELIQUIS-treated patients compared to 0.4% in those patients in the placebo group in the AMPLIFY-EXT study.

Bleeding results from the AMPLIFY-EXT study are summarized in Table 7.

Table 7: Bleeding Results in the AMPLIFY-EXT Study

	ELIQUIS 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Major	2 (0.2)	1 (0.1)	4 (0.5)
CRNM*	25 (3.0)	34 (4.2)	19 (2.3)
Major + CRNM	27 (3.2)	35 (4.3)	22 (2.7)
Minor	75 (8.9)	98 (12.1)	58 (7.0)
All	94 (11.2)	121 (14.9)	74 (9.0)

* CRNM = clinically relevant nonmajor bleeding.
Events associated with each endpoint were counted once per subject, but subjects may have contributed events to multiple endpoints.

Adverse reactions occurring in ≥1% of patients in the AMPLIFY-EXT study are listed in Table 8.

Table 8: Adverse Reactions Occurring in ≥1% of Patients Undergoing Extended Treatment for DVT and PE in the AMPLIFY-EXT Study

	ELIQUIS (apixaban) 2.5 mg bid N=840 n (%)	ELIQUIS 5 mg bid N=811 n (%)	Placebo N=826 n (%)
Epistaxis	13 (1.5)	29 (3.6)	9 (1.1)
Hematuria	12 (1.4)	17 (2.1)	9 (1.1)
Hematoma	13 (1.5)	16 (2.0)	10 (1.2)
Contusion	18 (2.1)	18 (2.2)	18 (2.2)
Gingival bleeding	12 (1.4)	9 (1.1)	3 (0.4)

Other Adverse Reactions

Less common adverse reactions in ELIQUIS-treated patients in the AMPLIFY or AMPLIFY-EXT studies occurring at a frequency of ≥0.1% to <1%:

Blood and lymphatic system disorders: hemorrhagic anemia

Gastrointestinal disorders: hematochezia, hemorrhoidal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, anal hemorrhage

Injury, poisoning, and procedural complications: wound hemorrhage, postprocedural hemorrhage, traumatic hematoma, periorbital hematoma

Musculoskeletal and connective tissue disorders: muscle hemorrhage

Reproductive system and breast disorders: vaginal hemorrhage, metrorrhagia, menometrorrhagia, genital hemorrhage

Vascular disorders: hemorrhage

Skin and subcutaneous tissue disorders: ecchymosis, skin hemorrhage, petechiae

Eye disorders: conjunctival hemorrhage, retinal hemorrhage, eye hemorrhage

Investigations: blood urine present, occult blood positive, occult blood, red blood cells urine positive

General disorders and administration-site conditions: injection-site hematoma, vessel puncture-site hematoma

DRUG INTERACTIONS

Apixaban is a substrate of both CYP3A4 and P-gp. Inhibitors of CYP3A4 and P-gp increase exposure to apixaban and increase the risk of bleeding. Inducers of CYP3A4 and P-gp decrease exposure to apixaban and increase the risk of stroke and other thromboembolic events.

Combined P-gp and Strong CYP3A4 Inhibitors

For patients receiving ELIQUIS 5 mg or 10 mg twice daily, the dose of ELIQUIS should be decreased by 50% when coadministered with drugs that are combined P-gp and strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, ritonavir) *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

For patients receiving ELIQUIS at a dose of 2.5 mg twice daily, avoid coadministration with combined P-gp and strong CYP3A4 inhibitors *[see Dosage and Administration (2.5) and Clinical Pharmacology (12.3) in full Prescribing Information]*.

Clarithromycin

Although clarithromycin is a combined P-gp and strong CYP3A4 inhibitor, pharmacokinetic data suggest that no dose adjustment is necessary with concomitant administration with ELIQUIS *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Combined P-gp and Strong CYP3A4 Inducers

Avoid concomitant use of ELIQUIS with combined P-gp and strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) because such drugs will decrease exposure to apixaban *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Anticoagulants and Antiplatelet Agents

Coadministration of antiplatelet agents, fibrinolytics, heparin, aspirin, and chronic NSAID use increases the risk of bleeding.

APPRAISE-2, a placebo-controlled clinical trial of ELIQUIS in high-risk, post-acute coronary syndrome patients treated with aspirin or the combination of aspirin and clopidogrel, was terminated early due to a higher rate of bleeding with ELIQUIS compared to placebo. The rate of ISTH major bleeding was 2.8% per year with ELIQUIS versus 0.6% per year with placebo in patients receiving single antiplatelet therapy and was 5.9% per year with ELIQUIS versus 2.5% per year with placebo in those receiving dual antiplatelet therapy.

In ARISTOTLE, concomitant use of aspirin increased the bleeding risk on ELIQUIS from 1.8% per year to 3.4% per year and concomitant use of aspirin and warfarin increased the bleeding risk from 2.7% per year to 4.6% per year. In this clinical trial, there was limited (2.3%) use of dual antiplatelet therapy with ELIQUIS.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The limited available data on ELIQUIS use in pregnant women are insufficient to inform drug-associated risks of major birth defects, miscarriage, or adverse developmental outcomes. Treatment may increase the risk of bleeding during pregnancy and delivery. In animal reproduction studies, no adverse developmental effects were seen when apixaban was administered to rats (orally), rabbits (intravenously) and mice (orally) during organogenesis at unbound apixaban exposure levels up to 4, 1 and 19 times, respectively, the human exposure based on area under plasma-concentration time curve (AUC) at the Maximum Recommended Human Dose (MRHD) of 5 mg twice daily.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Pregnancy confers an increased risk of thromboembolism that is higher for women with underlying thromboembolic disease and certain high-risk pregnancy conditions. Published data describe that women with a previous history of venous thrombosis are at high risk for recurrence during pregnancy.

Fetal/Neonatal adverse reactions

Use of anticoagulants, including ELIQUIS, may increase the risk of bleeding in the fetus and neonate.

Labor or delivery

All patients receiving anticoagulants, including pregnant women, are at risk for bleeding. ELIQUIS use during labor or delivery in women who are receiving neuraxial anesthesia may result in epidural or spinal hematomas. Consider use of a shorter acting anticoagulant as delivery approaches *[see Warnings and Precautions]*.

Data

Animal Data

No developmental toxicities were observed when apixaban was administered during organogenesis to rats (orally), rabbits (intravenously) and mice (orally) at unbound apixaban exposure levels 4, 1, and 19 times, respectively, the human exposures at the MRHD. There was no evidence of fetal bleeding, although conceptus exposure was confirmed in rats and rabbits. Oral administration of apixaban to rat dams from gestation day 6 through lactation day 21 at maternal unbound apixaban exposures ranging from 1.4 to 5 times the human exposures at the MRHD was not associated with reduced maternal mortality or reduced conceptus/neonatal viability, although increased incidences of peri-vaginal bleeding were observed in dams at all doses. There was no evidence of neonatal bleeding.

Lactation

Risk Summary

There are no data on the presence of apixaban or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Apixaban and/or its metabolites were present in the milk of rats (see Data). Because human exposure through milk is unknown, breastfeeding is not recommended during treatment with ELIQUIS (apixaban).

Data

Animal Data

Maximal plasma concentrations were observed after 30 minutes following a single oral administration of a 5 mg dose to lactating rats. Maximal milk concentrations were observed 6 hours after dosing. The milk to plasma AUC (0-24) ratio is 30:1 indicating that apixaban can accumulate in milk. The concentrations of apixaban in animal milk does not necessarily predict the concentration of drug in human milk.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total subjects in the ARISTOTLE and AVERROES clinical studies, >69% were 65 years of age and older, and >31% were 75 years of age and older. In the ADVANCE-1, ADVANCE-2, and ADVANCE-3 clinical studies, 50% of subjects were 65 years of age and older, while 16% were 75 years of age and older. In the AMPLIFY and AMPLIFY-EXT clinical studies, >32% of subjects were 65 years of age and older and >13% were 75 years of age and older. No clinically significant differences in safety or effectiveness were observed when comparing subjects in different age groups.

Renal Impairment

Reduction of Risk of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation

The recommended dose is 2.5 mg twice daily in patients with at least two of the following characteristics *[see Dosage and Administration (2.1) in full Prescribing Information]*:

- age greater than or equal to 80 years
- body weight less than or equal to 60 kg
- serum creatinine greater than or equal to 1.5 mg/dL

Patients with End-Stage Renal Disease on Dialysis

Clinical efficacy and safety studies with ELIQUIS did not enroll patients with end-stage renal disease (ESRD) on dialysis. In patients with ESRD maintained on intermittent hemodialysis, administration of ELIQUIS at the usually recommended dose *[see Dosage and Administration (2.1) in full Prescribing Information]* will result in concentrations of apixaban and pharmacodynamic activity similar to those observed in the ARISTOTLE study *[see Clinical Pharmacology (12.3) in full Prescribing Information]*. It is not known whether these concentrations will lead to similar stroke reduction and bleeding risk in patients with ESRD on dialysis as was seen in ARISTOTLE.

Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery, and Treatment of DVT and PE and Reduction in the Risk of Recurrence of DVT and PE

No dose adjustment is recommended for patients with renal impairment, including those with ESRD on dialysis *[see Dosage and Administration (2.1) in full Prescribing Information]*. Clinical efficacy and safety studies with ELIQUIS did not enroll patients with ESRD on dialysis or patients with a CrCl <15 mL/min; therefore, dosing recommendations are based on pharmacokinetic and pharmacodynamic (anti-FXa activity) data in subjects with ESRD maintained on dialysis *[see Clinical Pharmacology (12.3) in full Prescribing Information]*.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (Child-Pugh class A). Because patients with moderate hepatic impairment (Child-Pugh class B) may have intrinsic coagulation abnormalities and there is limited clinical experience with ELIQUIS in these patients, dosing recommendations cannot be provided *[see Clinical Pharmacology (12.2) in full Prescribing Information]*. ELIQUIS is not recommended in patients with severe hepatic impairment (Child-Pugh class C) *[see Clinical Pharmacology (12.2) in full Prescribing Information]*.

OVERDOSAGE

Overdose of ELIQUIS increases the risk of bleeding *[see Warnings and Precautions]*.

In controlled clinical trials, orally administered apixaban in healthy subjects at doses up to 50 mg daily for 3 to 7 days (25 mg twice daily for 7 days or 50 mg once daily for 3 days) had no clinically relevant adverse effects.

In healthy subjects, administration of activated charcoal 2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%, respectively. Thus, administration of activated charcoal may be useful in the management of ELIQUIS overdose or accidental ingestion. An agent to reverse the anti-factor Xa activity of apixaban is available.

PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide).

Advise patients of the following:

- Not to discontinue ELIQUIS without talking to their physician first.
- That it might take longer than usual for bleeding to stop, and they may bruise or bleed more easily when treated with ELIQUIS. Advise patients about how to recognize bleeding or symptoms of hypovolemia and of the urgent need to report any unusual bleeding to their physician.
- To tell their physicians and dentists they are taking ELIQUIS, and/or any other product known to affect bleeding (including nonprescription products, such as aspirin or NSAIDs), before any surgery or medical or dental procedure is scheduled and before any new drug is taken.
- If the patient is having neuraxial anesthesia or spinal puncture, inform the patient to watch for signs and symptoms of spinal or epidural hematomas *[see Warnings and Precautions]*. If any of these symptoms occur, advise the patient to seek emergent medical attention.
- To tell their physicians if they are pregnant or plan to become pregnant or are breastfeeding or intend to breastfeed during treatment with ELIQUIS *[see Use in Specific Populations]*.
- How to take ELIQUIS if they cannot swallow, or require a nasogastric tube *[see Dosage and Administration (2.6) in full Prescribing Information]*.
- What to do if a dose is missed *[see Dosage and Administration (2.2) in full Prescribing Information]*.

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Hospitalists are natural leaders in the COVID-19 battle

By Larry Beresford

Christopher Pribula, MD, a hospitalist at Sanford Broadway Medical Center in Fargo, N.D., didn't anticipate becoming his hospital's resident expert on COVID-19. Having just returned from vacation in March, he agreed to cover for a colleague on what would become the special care unit. "When our hospital medicine group decided that it would be the COVID unit, I just ran with it," he said. Dr. Pribula spent the next 18 days doing 8- to 14-hour shifts and learning as much as he could as the hospital – and the nation – wrestled with the pandemic.

"Because I was the first hospitalist, along with our infectious disease specialist, Dr. Avish Nagpal, to really engage with the virus, people came to me with their questions," Dr. Pribula said. Working to establish protocols for the care of COVID-19 patients involved a lot of planning, from nursing protocols to discharge planning.

Dr. Pribula was part of the hospital's incident command structure, thought about how the system could scale up for a potential surge, and worked with the North Dakota Medical Association to reach out to outlying medical centers on safety and infection control. He even drew on his prior work experience as a medical technologist doing negative-pressure containment in a cell-processing facility to help create the hospital's negative-pressure unit in an old ICU.

"We did a lot of communication from the start. To a certain extent we were making it up as we went along, but we sat down and huddled as a team every day at 9 and 4," he explained. "We started out with observation and retrospective research, and learned piece by piece. But that's how science works."

Hospitalists across the country have played leading roles in their hospitals' and health systems' response to the pandemic, and not just because they are on the front lines providing patient care. Their job as doctors who work full-time in the hospital makes them natural leaders in improving clinical quality and hospital administrative protocols as well as studying the latest information and educating their colleagues. Responding to the pandemic has required lots of planning, careful attention to schedules and assignments and staff stress, and working with other departments in the hospital and groups in the community, including public health authorities.

Current hospital treatment for COVID-19

As knowledge has grown, Dr. Pribula said, COVID-19 treatment in the hospital has come to incorporate remdesivir, a broad-spectrum antiviral; dexamethasone, a common steroid medication; and convalescent plasma, blood products from people who have recovered from the illness. "We went from no steroids to giving steroids. We went from putting patients on ventilators to avoid acute respiratory distress syndrome [ARDS] initially to now working to avoid intubation at all costs," he said.

"What we found is that we need to pressure-support these patients. We do proning and CPAP [continuous positive airway pressure] while we let the lungs heal. By the time they arrive at the hospital, more often than not they're on the backside of the viral load. But now we're dealing with the body's inflammatory response."

Navneet Attri, MD, a hospitalist at Sutter Santa Rosa (Calif.) Regional Hospital, 50 miles north of San Francisco, experienced fears and uncertainties working at a hospital that treated early COVID patients from the Grand Princess cruise ship. Early on, she wrote a post describing her experience for The Hospitalist Leader, the Society of Hospital Medicine's blog page.

Dr. Attri said she has gone through the gamut of emotions while caring for COVID-19 patients, addressing their fears and trying to support family members who aren't allowed to enter the hospital to be at their loved one's side. Sometimes, patient after patient with COVID-19 becomes almost too much. But seeing a lot of them in the intervening 6 months has increased her confidence level.

Understanding of how the disease is spread has continued to evolve, with a recent return to focusing on airborne transmission, she said. Frontline workers need N95 masks and eye shields, even if all of that personal protective equipment feels like a burden. Dr. Attri said she hardly notices the PPE anymore. "Putting it on is just a habit."

She sits on Sonoma County's COVID-19 surge planning group, which has representatives from the three local hospitals, the public health department, and other community agencies. "I report back to my hospitalist group about the situation in the community. Because our facilities were well prepared, our hospitals have not been overwhelmed," she said.

The importance of teamwork

Sunil Shah, MD, a hospitalist with Northwell Health's Southside Hospital in Bay Shore, N.Y., is part of the massive hospital medicine team, including reassigned specialists and volunteers from across the country, deployed at Northwell hospitals in Greater New York City and Long Island during the COVID-19 surge. Northwell probably has cared for more COVID-19 patients than any other health system in the country, and at the height of the surge the intensity of hospital care was like nothing he's ever seen. But he also expressed gratitude that doctors from other parts of the country were willing to come and help out.

Southside Hospital went almost overnight from a 200-bed acute facility to a full, 350-bed, regional COVID-19–only hospital. "On busy days, our entire hospital was like a floating ICU," he said. "You'd hear 'rapid response' or 'code blue' over the intercom every few seconds. Normally we'd have a designated rapid response person for the day, but with COVID, everybody stepped in to help – whoever was closest," he said.

Majid Sheikh, MD, a hospitalist at Emory University Hospital in Atlanta, also became a go-to COVID-19 expert for his group. "I didn't specifically volunteer, but my partner and I had the first cases, and the

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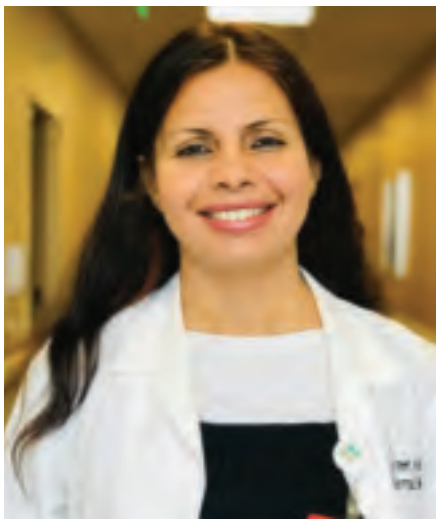
Dr. Pribula



Dr. Attri

Dr. Shah

Dr. Sheikh

Hospitalist Medicare payments are at risk for large cuts in 2021

Now is the time to act

By Ron Greeno, MD, FCCP, MHM

From the beginning, SHM has consciously and consistently taken a unique approach to its advocacy efforts with the federal government. The advocacy priorities of SHM most often concern issues that we feel have an impact on our patients and the broader delivery system, as opposed to a focus on issues that have direct financial benefit to our members.

This strategy has served SHM well. It has earned respect among policymakers and we have seen significant success for a young and relatively small medical society. The issues where we spend the bulk of our time and effort include advocating for issues like alternative payment models (APMs), which reward care quality as opposed to volume, as well as issues related to data integrity that APMs require. We have advocated strongly for changes to dysfunctional observation status rules, for workforce adequacy and sustainability, and for recognition of the importance of hospital medicine's contribution to the redesign of our nations delivery system. And SHM will continue to advocate for many other issues identified as being important to hospital medicine and our patients.

This year, for the first time in the two decades that I have served on the SHM Public Policy Committee, Medicare has proposed changes that would create unprecedented financial hardship for hospital medicine groups. Each year, as a part of its advocacy agenda, SHM reviews and comments on proposed changes to the Medicare Physician Fee Schedule (PFS). Among other things, the PFS adjusts payment rates to physicians for specific services. Changes under the PFS are required to be budget neutral. In effect, budget neutrality means that whenever certain services receive an increased payment rate, CMS is required to offset these changes by making cuts to other services. This year, in an effort to correct the long-standing underfunding of primary care services, CMS has increased payment for many Evaluation and Management (E&M) codes associated with outpatient primary care services. However, because of budget-neutrality requirements, many inpatient E&M care services will be receiving significant cuts.

The goal of increasing payment rates for primary care services is laudable, as many of these cognitive services have been long underfunded. However, the proposed payment increases will apply only to outpatient E&M codes and not their corresponding inpatient codes. While our outpatient Internal Medicine and Family Practice colleagues will benefit from these changes, inpatient providers, including hospitalists, stand to lose a significant amount revenue. SHM and the hospitalists we represent estimate that the proposed budget-neutrality adjustment will lead to an approximate 8% decrease in Medicare Fee for Services (FFS) revenue. Hospitalists are among the specialties that will be most impacted from these proposed changes. If put into effect, these proposals will leave hospital medicine behind.

These changes have been proposed at a time when hospitalists, along with their colleagues in critical care and emergency medicine, have been caring for patients on the frontlines of the COVID-19 pandemic at great risk to themselves and their families. While hospitalists are working tirelessly to provide lifesaving care to COVID-positive patients throughout the country, hospitalist groups have struggled financially as a result of the pandemic. Inpatient volumes, and therefore care reimbursement, has dropped significantly. Many hospitalists have already reported pay reductions of 20% or more. Others have seen their shifts reduced, resulting in understaffing, which may compromise the quality of care. For many groups, a Medicare reimbursement cut of this magnitude will not be financially sustainable.

SHM is, of course, fighting back. We are not asking CMS to completely abandon the increases in reimbursement for primary care outpatient codes, and we support properly valuing outpatient care services. However, we are asking CMS to find a solution that does not come at the expense of hospital medicine and the other specialties that care for acutely ill hospitalized patients, including patients with COVID-19.

Dr. Greeno is senior advisor for government affairs and past president of the Society of Hospital Medicine.

If a better solution requires holding off on the proposal for another year, CMS should do so. Furthermore, SHM is asking Congress to abandon the statutory requirement for budget neutrality in these extraordinary times as CMS and Congress work to find a solution that properly values both inpatient and outpatient care services.

To send a message to your representatives urging them to stop these payment cuts, please visit SHM's Legislative Action Center at www.votervoice.net/SHM/campaigns/77226/respond. You can read our full comments on the Medicare Physician Fee Schedule Proposed Rule at www.hospitalmedicine.org/policy--advocacy/letters/2021-physician-fee-schedule-proposed-rule/.

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leadership group was happy to have us there," he explained.

"One interesting thing I learned was the concept of the 'happy' hypoxemic patient, who is having a significant drop in oxygen saturation without developing any obvious signs of respiratory distress," he said. "We'd be checking the accuracy of the reading and trying to figure out if it was real." Emory was also one of the leaders in studying anticoagulant treatments for COVID-19 patients.

"Six months later I would say we're definitely getting better outcomes on the floor, and our COVID patients aren't landing in the ICU as easily," Dr. Sheikh said. "It was scary at first, and doubly scary when doctors sometimes don't feel they can say, 'Hey, I'm scared too,' or 'By the way, I really don't know what I'm doing.' So, we'd be trying to reassure the patients when the information was coming to us in fragments."

He also believes that the pandemic has afforded hospitalists the opportunity to be the clinical detectives they were trained to be. "I had to think more and really pay attention clinically in a much different way. You could say it was exciting and scary at the same time," he said.

A human fix in the hospital

Dr. Pribula agreed that the pandemic has been both a difficult experience and a rewarding one. "I think of the people I first admitted. If they had shown up even a month later, would they still be with us?" He believes that his group and his field are going to get to a place where they have solid treatment plans for how to provide optimal care and to protect providers from exposure.

One of the first COVID-19 patients in Fargo had dementia and was very distressed. "She had no idea why nobody was visiting or why we wouldn't let her out of her room," Dr. Pribula said. "Instead of reaching for sedatives, one of our nurses went into the room and talked with her, prayed a rosary, and played two hands of cards with her and didn't have to sedate her. That's what people need when they're alone and scared. It wasn't a medical fix but a human fix."

A version of this article originally appeared on Medscape.com.

COVID curriculum

Continued from page 1

as Zoom. Many of these changes were adopted even in settings with few actual COVID cases.

Medical students on clinical rotations were provided with virtual didactics when in-person clinical experiences were put on hold. In some cases, academic years ended early and fourth-year students graduated early so they might potentially join the hospital work force. Residents' assignments were also changed, perhaps seeing patients on non–COVID-19 units only or taking different shifts, assignments, or rotations. Public health or research projects replaced elective placements. New electives were created, along with journal clubs, online care conferences, and technology-facilitated, self-directed learning.

But every advancing medical student needs to rotate through an experience of taking care of real patients, said Amy Guiot, MD, MEd,

Dr. Vineet Arora

a hospitalist and associate director of medical student education in the division of hospital medicine at Cincinnati Children's Hospital Medical Center. "The Liaison Committee of Medical Education, jointly sponsored by the Association of American Medical Colleges and the American Medical Association, will not let you graduate a medical student without actual hands-on encounters with patients," she explained.

For future doctors, especially those pursuing internal medicine – many of whom will practice as hospitalists – their training can't duplicate "in the hospital" experiences except in the hospital, said Dr. Guiot, who is involved in pediatric training for medical students and residents from the University of Cincinnati.

For third- and fourth-year medical students, getting that personal contact with patients has been the hardest part, she added. But from March to May 2020, that experience was completely shut down at CCHMC, as at many medical schools, because of precautions aimed at preventing exposure to the novel coronavirus for both students and patients. That meant hospitals had to get creative, reshuffling schedules and the order of learning experiences; converting everything possible to virtual encounters on platforms such as Zoom; and reducing the length of rotations, the total number of in-person encounters, and the number of learners participating in an activity.

"We needed to use shift work for medical students, which hadn't been done before," Dr. Guiot said. Having students on different shifts, including nights, created more opportunities to fit clinical experiences into the schedule. The use of standardized patients – actors

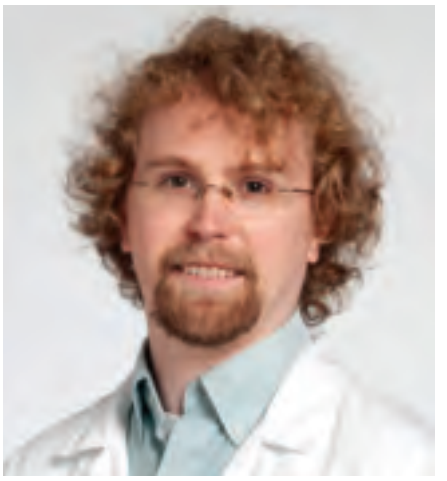
"We've also had to think differently and more creatively about how to get the same information across … In some cases, we saw that it was easier for learners to attend conferences and meetings online, with increased attendance for our events."

following a script who are examined by a student as part of learning how to do a physical exam – was also put on hold.

"Now we're starting to get it back, but maybe not as often," she said. "The actor wears a mask. The student wears a mask and shield. But it's been harder for us to find actors – who tend to be older adults who may fear coming to the medical center – to perform their role, teaching medical students the art of examining a patient."

A return to basics

The COVID-19 pandemic forced medical schools to get back to basics, figuring out the key competencies students needed to learn, said Alison Whelan, MD, AAMC's chief medical education officer. Both medical schools and residency programs needed to respond quickly and in new ways, including with course



Dr. Marc Miller

"Because pediatrics is so family centered, talking to patients and families at the bedside is highly valued. So we had virtual sessions talking about how to do that, with videos to illustrate it put out by Cincinnati Children's Hospital."

content that would teach students about the virus and its management and treatment.

Schools have faced crises before, responding in real time to SARS (severe acute respiratory syndrome), Ebola, HIV, and natural disasters, Dr. Whelan said. "But there was a nimbleness and rapidity of adapting to COVID – with a lot of sharing of curriculums among medical colleges." Back in late March, AAMC put out guidelines that recommended removing students from direct patient contact – not just for the student's protection but for the community's. A subsequent guidance, released Aug. 14, emphasized the need for medical schools to continue medical education – with appropriate attention to safety and local conditions while working closely with clinical partners.

Dr. Guiot, with her colleague Leslie Farrell, MD, and four very creative medical students, developed an online fourth-year elective course for University of Cincinnati medical students, offered asynchronously. It aimed to transmit a comprehensive understanding of COVID-19 and its virology, transmission, clinical prevention, diagnosis, and treatment, as well as to examine national and international responses to the pandemic and their consequences and related issues of race, ethnicity, socioeconomic status, and health disparities. "We used several articles from the Journal of Hospital Medicine for students to read and discuss," Dr. Guiot said.

Christopher Sankey, MD, SFHM, associate program director of the traditional internal medicine residency program and associate professor of medicine at Yale University, New Haven, Conn., oversees the inpatient educational experience for internal medicine residents at Yale. "As with most programs, there was a lot of trepidation as we made the transition from in-person to virtual education," he said.

The two principal, non–ward-based educational opportunities for the Yale residents are morning report, which involves a case-based discussion of various medical issues, usually led by a chief resident, and noon conference, which is more didactic and content based. Both made the transition to virtual meetings for residents.

"We wondered, could these still be well-attended, well-liked, and successful learning experiences if offered virtually? What I found when I surveyed our residents was that the virtual conferences were not only well received, but actually preferred," Dr. Sankey said. "We have a large campus with lots of internal medicine services, so it's hard to assemble everyone for meetings. There were also situations in which there were so many residents that they couldn't all fit into the same room." Zoom, the virtual platform of choice, has actually increased attendance.

Marc Miller, MD, a pediatric hospitalist at the Cleveland Clinic, helped his team develop a virtual curriculum in pediatrics presented to third-year medical students during the month of May, when medical students were being taken off the wards. "Some third-year students still needed to get their pediatric clerkships done. We had to balance clinical exposure with a lot of other things," he explained.

The curriculum included a focus on interprofessional aspects of interdisciplinary, family-centered bedside rounds; a COVID literature review; and a lot of case-based scenarios. "Most challenging was how to remake family rounds. We tried to incorporate students into table rounds, but that didn't feel as valuable," Dr. Miller said. "Because pedi-

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Dr. Christopher Sankey

Dr. Alison Whelan

The COVID-19 pandemic forced medical schools to get back to basics, figuring out the key competencies students needed to learn. "There was a nimbleness and rapidity of adapting to COVID – with a lot of sharing of curriculums among medical colleges."

atrics is so family centered, talking to patients and families at the bedside is highly valued. So we had virtual sessions talking about how to do that, with videos to illustrate it put out by Cincinnati Children's Hospital."

The most interactive sessions got the best feedback, but all the sessions went over very well, Dr. Miller said. "Larger lessons from COVID include things we already knew, but now with extra importance, such as the need to encourage interactivity to get students to buy in and take part in these conversations – whatever the structure."

Vineet Arora, MD, MHM, an academic hospitalist and chief medical officer for the clinical learning environment at the University of Chicago, said that the changes wrought by COVID have also produced unexpected gains for medical education. "We've also had to think differently and more creatively about how to get the same information across in this new environment," she explained. "In some cases, we saw that it was easier for learners to attend conferences and meetings online, with increased attendance for our events." That includes participation on quality improvement committees, and attending online medical conferences presented locally and regionally.

"Another question: How do we teach interdisciplinary rounds and how to work with other members of the team without having face-to-face interactions?" Dr. Arora said. "Our old interdisciplinary rounding model had to change. It forced us to rethink how to create that kind of learning. We can't have as many people in the patient's room at one time. Can there be a physically distanced 'touch-base' with the nurse outside the patient's room after a doctor has gone in to meet the patient?"

Transformational change

In a recent JAMA Viewpoint column, Catherine R. Lucey, MD, and S. Claiborne Johnston, MD, PhD,[1] called the impact of COVID-19 "transformational," in line with changes in medical curriculums recommended by the 2010 Global Independent Commission on Education of Health Professionals for the 21st Century,[2] which asserted that the purpose of professional education is to improve the health of communities.

The authors stated that COVID-19 brought clarity and urgency to this purpose, and will someday be viewed as a catalyst for the needed transformation of medical education as medical schools embarked on curriculum redesign to embrace new competencies for current health challenges.

They suggested that medical students not only continued to learn during the COVID crisis "but in many circumstances, accelerated their attainment of the types of competencies that 21st century physicians must master." Emerging competencies identified by Dr. Lucey and Dr. Johnston include:

- Being able to address population and public health issues
- Designing and continuously improving the health care system
- Incorporating data and technology in service to patient care, research, and education
- Eliminating health care disparities and discrimination in medicine
- Adapting the curriculum to current issues in real time
- Engaging in crisis communication and active change leadership

How is the curriculum changing? It's still a work in progress. "After the disruptions of the spring and summer, schools are now trying to figure which of the changes should stay," said Dr. Whelan. "The virus has also highlighted other crises, with social determinants of health and racial disparities becoming more front and center. In terms of content, medical educators are rethinking a lot of things – in a good way."

Another important trend cast in sharper relief by the pandemic is a gradual evolution toward competency-based education and how to assess when someone is ready to be a doctor, Dr. Whelan said. "There's been an accelerated consideration of how to be sure each student is competent to practice medicine."[3]

Many practicing physicians and students were redeployed in the crisis, she said. Pediatric physicians were asked to take care of adult patients, and internists were drafted to work in the ICU. Hospitals quickly developed refresher courses and competency-based assessments to facilitate these redeployments. What can be learned from such on-the-fly assessments? What was needed to make a pediatrician, under the supervision of an internist, able to take good care of adult patients?

And does competency-based assessment point toward some kind of time-variable graduate medical education of the future – with graduation when the competencies are achieved, rather than just tethered to time- and case volume–based requirements? It seems Canada is moving in this direction, and COVID might catalyze a similar transformation in the United States.[3]

Change in the curriculum

Does the content of the curriculum for preparing future hospitalists need to change significantly? "My honest answer is yes and no," Dr. Sankey said. "One thing we found in our training program is that it's possible to become consumed by this pandemic. We need to educate residents about it, but future doctors still need to learn a lot of other things. Heart failure has not gone away.

"It's okay to stick to the general curriculum, but with a wider variety of learning opportunities. Adding content sessions on population health, social determinants of health, race and bias, and equity is a start, but it's by no means sufficient to give these topics the importance they deserve. We need to interpolate these subjects into sessions we're already doing," he said. "It is not enough to do a couple of lectures on diversity. We need to weave these concepts into the education we provide for residents every day.

"I think the pandemic has posed an opportunity to critically consider what's the ideal teaching and learning environment. How can we make it better? Societal events around race have demonstrated essential areas for curricular development, and the pandemic had us primed and already thinking about how we educate future doctors – both in terms of medium and content," he said.

Some medical schools started their new academic year in July; others put it off until September. Patient care at CCHMC is nearly back to where it used to be before COVID-19 began, Dr. Guiot said in a September interview, "but in masks and goggles." As a result, hospitals are having to get creative all over again to accommodate medical students.

"I am amazed at the camaraderie of hospitals and medical schools, trying to support our learners in the midst of the pandemic," she said. "I learned that we can be more adaptive than I ever imagined. We were all nervous about the risks, but we learned how to support each other and still provide excellent care in the midst of the pandemic. We're forever changed. We also learned how to present didactics on Zoom, but that was the easy part."

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13 best practices to improve hospitalist billing

Favor solutions that benefit patients

By Angela Mirabella, BA; Ilene Rosenberg, MD; Corey Kiassat, PhD, MBA

As an aspiring physician, I like learning about how things work. Since medical students learn very little about the "business" of medicine in school, this led me to pioneer a project on missed billing by hospitalists at a medium-sized hospital in the northeastern United States. Although hospitalists do a tremendous amount of work, they do not always bill for what they are doing. The question became: Why are hospitalists missing charges and what can we do to stop it?

Shortly into my study, I recognized there was little daily communication between the administrators and the hospitalists; neither the hospitalists nor administrators understood the different dynamics that the others faced in their own workplace. It became apparent that administrators needed to learn what was important to hospitalists and to address them at their level in order to bring about change.

The hospitalists who had the highest billing performances were more likely to start writing notes and charge earlier while rounding.

Some trending themes emerged as I started shadowing the hospitalists. Many of them asked how this project would benefit them. They argued that administrative needs should be dealt with at the administrative level. A major point was made that current incentives, such as the bonuses given for exceeding a certain number of RVUs, were not the motivating force behind their work ethics. From my observations, the motivating factors were the quality of their patient care, the needs of their patients, and teaching. The hospitalists also were eager to teach and continually instructed me on clinical skills and how to be a better medical student.

Bonuses or notoriety didn't seem to be the main incentives for them. However, efficiency – especially in rounding – was important, and that became the focal point of the project. I found several studies that showed that improvements in aspects of rounding led to increased quality of patient care, decreased burnout, increased patient satisfaction, and decreased workload and discussed some of those findings with the hospitalists.[1-10] When the hospitalists felt that their concerns were being heard, they became even more involved in the project, and the administrators and hospitalists started working together as a team.

One hospitalist spent 2 hours helping me design the platform that would be used for hospitalists to report barriers in their rounding process that may cause them to miss a charge. Once we identified those barriers, we discussed the possibility of standardizing their workflow based off these data. Many hospitalists argued that each physician has unique skills and practices that make them successful; therefore, the disruption of an already established workflow may cause a decrease in efficiency.

The hospitalists and I talked a lot about the importance of them rounding more efficiently and how that could positively affect the time that they have with their patients and themselves. We discussed that, because of the additional work missed billing causes, minimizing this burden can possibly help decrease burnout. As a result, seven hospitalists, the administrative staff, and I met and created 13 best practices, 6 of which they were able to get approved to use immediately. To note, hospitalists bill differently; some use a software company, fill out paper forms still, or have integration within their EMR. Although these solutions were made for a program which has the ability to bill within the EMR, many of the principles will apply to your program too.

The 13 best practices that the seven hospitalists agreed upon are the following:

1 Set up so that, when a doctor signs a note, it opens a charge option or there is a hard stop.

2 Have charge delinquencies sent via email to the hospitalist.

3 Standardize that hospitalists charge directly after writing a note consistently as part of their workflow.*

Ms. Mirabella attends the Frank H. Netter MD School of Medicine at Quinnipiac University, Hamden, Conn., in the class of 2022. She has interests in internal/hospital medicine, primary care, and health management and leadership. Dr. Rosenberg is associate professor at the Frank H. Netter MD School of Medicine at Quinnipiac University where she is director of clinical skills coaching. Dr. Kiassat is associate dean of the School of Engineering and associate clinical professor at Frank H. Netter MD School of Medicine, at Quinnipiac University. His research interests are in process improvement in health care, using Lean Six Sigma.

4 Prioritize discharges before rounding.*

5 Standardize the use of the "my prof charges" column, a feature of this hospital's EMR system that tells them if they had made a charge to a patient or not, in order to remind them to/confirm billing a patient.*

6 Create reports by the EMR system to provide charge data for individual providers.

7 Create a report for bill vs. note to help providers self-audit. At this hospital, this feature was offered to the administrators as a way to audit their providers and doctors.

8 Ensure that, when a patient is seen by a physician hospitalist as well as an NP/PA hospitalist, the appropriate charge for the physician is entered.

9 Send notifications to the physician hospitalist if a charge gets deleted by another person (e.g., NP/PA hospitalist).

10 Send handoff of daily rounding sheets, or a paper copy of the patients assigned to a hospitalist for his/her shift, at the end of the shift to the project specialist.*

11 Keep the rounding sheets a complete and accurate account of the patients seen by the hospitalist.*

12 Complete and check all billing at the end of hospitalist's shift at the latest.*

13 Participate on Provider Efficiency Training to optimize workflow, by creating more efficient note-writing behavior using Dragon.

**Indicates the practices the hospitalists were able to implement immediately. Practices 1, 2, 6, 7, and 9 request EMR changes. Practice 8 was already an established practice the hospitalists wished to continue. Practice 13 was suggested by the Lean Director for the continuation of a previous project.*

Six of the best practices were easier to implement right away because they were at the discretion of the hospitalists. We found that the hospitalists who had the highest billing performances were more likely to start writing notes and charge earlier while rounding. Those who had poorer billing performances were more likely to leave all note writing and billing toward the end of their shift. The few exceptions (hospitalists who left all note writing and charging to the end of their shift yet had high billing performances) were found to have a consistent and standardized workflow. This was unlike the hospitalists who had the lowest billing performances. Having practices that help remind hospitalists to bill will surely help prevent

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When the hospitalists felt that their concerns were being heard, they became even more involved in the project, and the administrators and hospitalists started working together as a team.

missed billing, but because of the findings from this project, it was important to have consistent and standardized practices to additionally improve missed billing.

When we followed up with the hospitalist division 2 months later, we learned they were making great progress. Not only were hospitalists using their best practices, but in working with the administrators, they were designing sessions to further educate fellow hospitalists to prevent further missed billing. These sessions outlined shortcuts, resources, and ways hospitalists may modify their personal EMR accounts to prevent missed billing. None of the progress could have been made without first understanding and addressing what is truly important to the hospitalists.

In summary, we noted these general observations in this project:

- Hospitalists favor solutions that benefit them or their patients.
- Hospitalists want to be part of the solution process.
- Hospitalists were more likely to accept ideas to improve their rounding if it meant they could keep their routine.

Obstacles exist in our health care system that prevent administrators and hospitalists from working together as a team. The more we are able to communicate and collaborate to fix problems in the health system, the more we can use the system to our mutual advantage. With the ongoing changes in medicine, especially during uncertain times, better communication needs be a major priority to affect positive change.

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How much longer?

SHM has changed direction as needed during the pandemic

By Eric Howell, MD, MHM

"How much longer?" As a kid, I can remember the long holiday car ride with my parents from my home in Annapolis, Md., to Upstate New York where my grandparents lived. At the time, the ride felt like an eternity: endless miles of frozen landscape, limited food, and a brother who constantly crossed over the invisible line that was my side of the car.

We made our parents crazy asking, "how much longer?" every few minutes. This was the late 1970s, with no GPS or Google Maps to give you arrival times to the minute, traffic warnings, or reroutes when the inevitable delays occurred. We just plowed ahead, and my parents' answer was always something vague like, "in a few hours" or "we're about halfway through." They did not know when we'd arrive with certainty either.

We at SHM have that same feeling about the pandemic. How much longer? No one can tell us when the COVID-19 threat will abate. The experts' answers are understandably vague, and the tools for forecasting are nonexistent. Months? That is the best we know for now.

At SHM, we believe we will make it through this journey by adapting to roadblocks, providing tools for success to our professional community, and identifying opportunities for us to connect with each other, even if that means virtually.

Our work on resources for quality improvement; the opioid epidemic; well-being, diversity, equity, and inclusion; leadership; professional development; advocacy; and so much more is as active as ever.

Like the rest of the planet, the spring of 2020 hit SHM with a shock. Hospital Medicine 2020 (HM20) in San Diego was shaping up to be the largest Annual Conference SHM ever had, the Pediatric Hospital Medicine 2020 (PHM20) conference was well planned and expected to be a huge success, regional SHM chapters were meeting (and growing), and membership was thriving. I was transitioning out of my roles at Johns Hopkins and looking forward to my new role as CEO of SHM. All in all, March 2020 began with a fantastic outlook.

Wow, what a difference a few weeks made. We watched as the pandemic spread across regions of the country, concerned for the well-being of our patients and our hospitalists. We saw how our members were at the forefront of patient care during this crisis and understood that SHM had to adapt rapidly to meet their needs in real time.

By May, SHM had canceled HM20, Chapter activity was halted, PHM20 was on its way to being canceled, SHM committee work was put on hold, and I was spending my last few months at Hopkins as the chief medical officer at the Baltimore Convention Center Field Hospital (which we got up and running in less than a month)! Whew.

But just like my dad could pivot our 1970s Chevy station wagon around a traffic jam in a flash, so too did SHM leadership start navigating around the COVID-19 landscape. As soon as HM20 was canceled, SHM immediately began planning for a virtual offering in August. We had hoped to attract at least 100 attendees and we were thrilled to have more than 1,000! PHM20 was switched from an in-person to a virtual meeting with 634 attendees. We launched numerous COVID-19 webinars and made our clinical and educational offerings open access. Our Public Policy Committee was active around both COVID-19 and hospitalist-related topics – immigration, telehealth, well-being, and financial impacts, to name a few. (And I even met with the President of the United States and advocated for personal protective equipment.) The *Journal of Hospital Medicine* worked with authors to get important publications out at record speed. And of course, *The Hospitalist* connected all of us to our professional leaders and experts.

By the fall of 2020, SHM had actively adjusted to the "new normal" of this pandemic: SHM staff have settled into their new "work from home" environments, SHM Chapters are connecting members in the virtual world, SHM's 2021 Annual Conference will be all virtual – rebranded as "SHM Converge" – and the *State of Hospital Medicine* Report (our every-other-year source for trends in hospital medicine) now has a COVID-19 supplement, which was developed at lightning speed. Even our SHM Board of Directors is meeting virtually! All this while advancing the routine work at SHM, which never faltered. Our work on resources for quality improvement; the opioid epidemic; well-being, diversity, equity, and inclusion (DEI); leadership; professional development; advocacy; and so much more is as active as ever.

I don't know how much longer we have on this very long pandemic journey, so I'll use my father's answer of "we're about halfway through." We have been immersed in it for months already, with months still ahead. But regardless of the upcoming twists and turns COVID-19 forces you, our patients, and our larger society to take, SHM is ready to change direction faster than a 1970s Chevy.

The SHM staff, leadership, and members will be sure that hospitalists receive the tools to navigate these unprecedented times. Our patients need our skills to get through this as safely as possible. While we may not be able to tell them "how much longer," we can certainly be prepared for the long road ahead as we begin 2021.

Dr. Howell is CEO of the Society of Hospital Medicine.

The top pediatric articles of 2019

Updates in pediatric hospital medicine

By Christopher J. Russo, MD; Nathan M. Money, MD; Maura A. Steed, MD

Dr. Russo is director of pediatrics, medical director for quality and innovation, at WellSpan Health, York, Pa. Dr. Money is a pediatric hospitalist at Primary Children's Hospital, University of Utah School of Medicine, Salt Lake City. Dr. Steed is instructor of hospital medicine, Northwestern Memorial Hospital and Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University School of Medicine, Chicago. *The authors would like to thank Klint M. Schwenk, MD, and the Society for Hospital Medicine Pediatric Special Interest Group Executive Council.*

The expansion of the field of pediatric hospital medicine in the past 30 years has resulted in improved health care outcomes for hospitalized children[1,2] and has been accompanied by a robust increase in the amount of scholarly work related to the field.[3] We performed a review of the literature published in 2019 to identify the 10 articles that had the most impact on pediatric hospital medicine, and presented the findings at HM20 Virtual, the 2020 annual conference of the Society of Hospital Medicine. Five of the selected articles are highlighted here.

STUDY 1

Wechsler ME et al. Step-up therapy in Black children and adults with poorly controlled asthma. N Engl J Med. 2019 Sep 26;381(13):1227-39.

Background

Current pediatric asthma guidelines suggest adding a long-acting beta-agonist (LABA) to inhaled corticosteroid (ICS) therapy, rather than increasing the ICS dose, for children with poorly controlled asthma. However, these data are based on trials with disproportionately few Black subjects. This study aimed to determine the best step-up therapy for Black patients whose asthma was poorly controlled on ICS monotherapy.

Study overview and results

The authors reported two parallel double-blind, randomized, controlled trials, one in children and one in adolescents and adults. The study of children included 280 subjects ranging in age from 5 to 11, with at least one Black grandparent, and with poorly controlled asthma on low-dose ICS therapy. It used a four-way crossover design in which each subject was treated with four different 14-week treatment regimens: either double (medium-dose) or quintuple (high-dose) their baseline ICS dose, with or without the addition of a LABA. A superior response was defined by the composite outcome of at least one fewer asthma exacerbation, more asthma-control days, or a 5–percentage point difference in predicted forced expiratory volume in 1 second (FEV_1). Forty-six percent of children had improved asthma outcomes when the ICS dose was increased rather than with the addition of a LABA. In contrast, Black adolescents and Black adults had superior responses to the addition of a LABA. There was no significant interaction between the percentage of African ancestry as determined by DNA genotyping and the primary composite outcome. High-dose ICS was associated with a decrease in the ratio of urinary cortisol to creatinine in children younger than 8 years.

Limitations

Approximately 25% of children dropped out of the study, with disproportionately more children dropping out while on a high-dose ICS regimen. Additionally, the difference in the composite outcome was primarily driven by differences in FEV_1, with few subjects demonstrating a difference in asthma exacerbations or asthma-control days. Although a decrease in urinary cortisol to creatinine ratio was noted in children under 8 on high-dose ICS, the study period was not long enough to determine the clinical implications of this finding.

Important findings and implications

While studies with a majority of White children have suggested a superior response from adding a LABA compared to increasing the dose of an ICS, almost half of Black children showed a superior response when the dose of an ICS was increased rather than adding a LABA. It is important to note that current guidelines are based on studies with a disproportionate majority of White subjects and may not accurately reflect optimal care for patients in other racial groups. This study underscores the need to include a diverse patient population in research studies.

STUDY 2

Chang PW; Newman TB. A simpler prediction rule for rebound hyperbilirubinemia. Pediatrics. 2019 Jul;144(1):e20183712.

Background

Hyperbilirubinemia (jaundice) is estimated to affect 50%-60% of all newborns. Rebound hyperbilirubinemia – a rise in bilirubin after cessation of phototherapy – is common and can lead to recently discharged infants being readmitted for additional therapy. Lack of clear guidelines regarding when to discharge infants with hyperbilirubinemia has likely contributed to practice variation and some trepidation regarding whether a bilirubin level is "low enough" to discontinue therapy.

Study overview and results

The authors had previously proposed a three-factor hyperbilirubinemia risk model and sought to simplify their rule further.[4] They examined a retrospective cohort of 7,048 infants greater than or equal to 35 weeks' gestation using a random split sample. The authors derived a two-factor model using the same methods and compared its performance to the three-factor model. The two-factor formula was shown to be a good fit as a logistic regression model (Hosmer-Lemeshow test 9.21; $P = .33$), and the AUROC (area under the receiver operating characteristic) curves for the derivation and validation cohorts were similar between the two-factor (0.877 and 0.876, respectively) and three-factor (0.887 and 0.881, respectively) risk models.

Limitations

These data are limited to infants receiving their first treatment of phototherapy and have not been externally validated. An important variable, serum bilirubin at phototherapy termination, was estimated in most subjects, which may have affected the accuracy of the prediction rule. Whether infants received home phototherapy was based only on equipment orders, and some infants may have received phototherapy unbeknownst to investigators. Last, infants with rebound hyperbilirubinemia at less than 72 hours after phototherapy discontinuation may have been missed.

Important findings and implications

This prediction model provides evidence-based, concrete data that can be used in making joint decisions with families regarding discharge timing of infants with hyperbilirubinemia. It also could be beneficial when deciding appropriate follow-up time after discharge.

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STUDY 3

Ramgopal S et al. Risk of serious bacterial infection in infants aged ≤60 days presenting to emergency departments with a history of fever only. J Pediatr. 2019 Jan;204:191-95. doi: 10.1016/j.jpeds.2018.08.043.

Background

Febrile infants aged 60 days and younger are at risk for serious bacterial infections (SBI) including urinary tract infections (UTI), bacteremia, and meningitis. As physical exam is a poor discriminator of SBI in this age group, providers frequently rely on laboratory values and risk factors to guide management. Infants presenting with documented fevers by caregivers but found to have no fever in the emergency department are a challenge, and there are limited data regarding SBI frequency in this population.

Study overview and results

The authors performed a secondary analysis of a prospectively gathered cohort of infants aged 60 days and younger within the Pediatric Emergency Care Applied Research Network (PECARN) who had blood, urine, and cerebrospinal fluid (CSF) data available. Notable exclusions included infants who were premature; had a focal infection; were clinically ill; had recent antibiotic use, did not have blood, urine, and CSF data available; or were lost to telephone follow-up at 7 days to ensure wellness. The study cohort included 6,014 infants, 1,233 (32%) who were febrile by history alone. Rates of overall SBI were lower in the afebrile group (8.8% vs. 12.8%). For infants 0-28 days, rates of UTI were lower for the afebrile group (9.5% vs. 14.5%), but there was no difference in the rates of bacteremia or meningitis. For infants 29-60 days, rates of UTI (6.6% vs. 9.3%) and bacteremia (.5% vs. 1.7%) were lower in the afebrile group.

Limitations

Neither the use of home antipyretics nor the method of temperature taking at home were studied. Also, as this was a secondary analysis, it is possible that not all infants who presented with history of fever only were captured, as work-up was dictated by individual treating providers who may have chosen not to work up certain afebrile infants.

Important findings and implications

Nearly one-third of infants presenting for fever evaluation are afebrile on arrival. Although overall rates of SBI were lower in the group with fever by history only, this difference is largely accounted for by differing rates of UTI. Rates of bacteremia and meningitis remained substantial between groups, particularly for infants aged 0-28 days. Because of the significant morbidity associated with these infections, it is reasonable to suggest that absence of fever on presentation alone should not alter clinical or laboratory work-up, particularly in infants 0-28 days.

STUDY 4

Humphrey-Murto S et al. The influence of prior performance information on ratings of current performance and implications for learner handover: A scoping review. Acad Med. 2019 Jul;94(7):1050-7.

Background

Learner handover (LH) or "forward feeding" occurs when information about trainees is shared between faculty supervisors. Although this can be helpful to tailor educational experiences and build upon previous assessments, it risks stigmatizing trainees and adding bias to future feedback and assessments as the trainee never really has a "clean slate." In this study, the authors sought to uncover the key concepts of how prior performance information (PPI) influences assessments and any implications for medical education.

Study overview and results

The authors performed a cross-disciplinary scoping review looking at over 17,000 articles published between 1980 and 2017 across the domains of psychology, sports, business, and education. Seven themes were identified with the following notable findings. Raters exposed to positive PPI scored a learner's performance higher, and vice versa. There was a dose-response relationship with more positive and more negative PPI resulting in higher and lower assessments, respectively. General standards, such as a direction to complete all work in a timely manner, caused an assimilation effect, while specific standards, such as a direction to complete a certain task by a certain day, did not. More motivated and more experienced raters are less affected by PPI, and those who believe that people can change (incremental theorists) are less affected by PPI while those who believe personal attributes are fixed (entity theorists) are more affected.

Limitations

The heterogeneity of the studies and the fact that they were largely conducted in experimental settings may limit generalizability to medical education. Slightly less than half of the studies included a control arm. Last, most of the studies looked at the ratings of only one target performance, not multiple performances over time.

Important findings and implications

Ratings of current performance displace toward PPI direction, with negative PPI more influential than positive PPI. In a formative setting, PPI may help the assessor focus on areas of possible weakness. In contrast, for a summative assessment, PPI may be prejudicial and have an impact on the rating given to the student. Clinicians should be mindful of the information they share with future raters about learners and the potential bias on future assessments that can manifest as a result.

STUDY 5

McCann ME et al. Neurodevelopmental outcome at 5 years of age after general anaesthesia or awake-regional anaesthesia in infancy (GAS): An international, multicentre, randomised, controlled equivalence trial. Lancet. 2019 Feb;393:664-77.

Background

Animal models and observational studies have suggested a link between early anesthesia exposure and adverse neurocognitive outcomes; however, findings have been mixed and studies are prone to confounding. This study is the first randomized controlled trial to compare neurocognitive outcomes for infants exposed to general anesthesia versus awake-regional anesthesia.

Study overview and results

In this international, multicenter, assessor-masked trial, 722 infants undergoing inguinal hernia repair were randomized to awake-regional anesthesia or single-agent sevoflurane-based general anesthesia. Infants born at greater than 26 weeks' gestational age were eligible, while those with prior anesthesia exposure or risks for neurocognitive delay were excluded. The primary outcome was full-scale intelligence quotient (FSIQ) testing at 5 years of age on the Wechsler Preschool and Primary Scale of Intelligence, third edition (WPPSI-III). Seven additional neurodevelopmental assessments and parental questionnaires regarding behavior were administered as secondary outcomes. Average anesthesia exposure was 54 minutes, and no infant had exposure greater than 120 minutes. There was no significant difference in mean scores on WPPSI-III FSIQ testing, and no difference in the additional neurocognitive assessments or parent-reported outcomes used as secondary outcomes.

Limitations

This study was limited to single, short periods of single-agent anesthesia exposure in children with no additional neurologic risk factors, so caution should be used in extrapolating these data to children with medical complexity and children undergoing multiple procedures, longer surgeries, or multidrug anesthetic regimens. The study population was majority male because of the surgical pathology selected and included only children in the narrow range of postmenstrual age 60 weeks or less. While this population represents a suspected period of high cerebral vulnerability based on animal models, the implications of anesthesia exposure at other ages are unclear.

Important findings and implications

An estimated 10% of children from developed countries are exposed to general anesthesia during the first 3 years of life. While hospitalists do not typically select the route of anesthesia, they frequently care for patients undergoing procedures and must address parental concerns regarding the safety of anesthesia exposure. Given the rigorous study methods and long-term follow up in the current study, these data should provide reassurance that, for healthy infants undergoing short, single-agent anesthetic exposure, there is no evidence of future adverse neurologic outcomes.

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Bias against hiring hospitalists trained in family medicine still persists

Outdated perceptions of family medicine

By Jeff Craven
MDedge News

A family medicine–trained doctor, fresh out of residency, visits a career website to scout out prospective hospitalist jobs in their region. As they scroll through the job listings, they come across one opportunity at a nearby hospital system that seems like a good fit. The listing offers a competitive salary and comprehensive benefits for the position, and mentions hospitalists in the department will have the opportunity to teach medical students.

The only problem? The position is for internal medicine–trained doctors only. After searching through several more listings with the same internal medicine requirement, the family medicine doctor realizes the pool of jobs doctor seems much smaller.

When Robert M. Wachter, MD, MHM, and Lee Goldman, MD, coined the term "hospitalist" in a 1996 New England Journal of Medicine article, hospitalists were primarily clinicians with an internal medicine background, filling the gap created by family medicine doctors who increasingly devoted their time to patients in their practice and spent less time rounding in the hospital.

As family medicine doctors have returned to hospital medicine, it has become difficult to find positions as hospitalists because of a preference by some recruiters and employers that favors internal medicine physicians over those who are trained in family medicine. The preference for internal medicine physicians is sometimes overt, such as a requirement on a job application. But the preference can also surface after a physician has already applied for a position, and they will then discover a recruiter is actually looking for someone with a background in internal medicine. In other cases, family medicine physicians find out after applying that applicants with a background in family medicine are considered, but they're expected to have additional training or certification not listed on the job application.

The situation can even be as stark as a hospital system hiring an internal medicine doctor just out of residency over a family medicine doctor with years of experience as a board-certified physician. Hiring practices in large systems across multiple states sometimes don't just favor internal medicine, they are entirely focused on internal medicine hospitalists, said experts who spoke with *The Hospitalist*.

Understanding outdated perceptions

Victoria McCurry, MD, current chair of the Society of Hospital Medicine's family medicine Special Interest Group (SIG) Executive Committee and Faculty Director of Inpatient Services at UPMC McKeesport (Pa.)

Dr. McCurry

Family Medicine Residency, said hearsay inside the family medicine community influenced her first job search looking for hospitalist positions as a family medicine physician.

"I was intentional about choosing places that I assumed would be open to family medicine," she said. "I avoided the downtown urban academic hospitals, the ones that had a large internal medicine residency and fellowship presence, because I assumed that they would not hire me.

"There's a recognition that, depending on the system that you're in and their history with family medicine–trained hospitalists, it can be difficult as a family physician to seek employment," Dr. McCurry said.

"When I graduated from my residency in 2014, I did not have the same opportunities to be a hospitalist as an internal medicine resident would have," said Shyam Odeti, MD, a family practice–trained hospitalist who works at Ballad Health in Johnson City, Tenn. "The perception is family medicine physicians are not trained for hospitalist practice. It's an old perception."

This perception may have to do with the mindset of the leadership where a doctor has had residency training, according to Usman Chaudhry, MD, a family medicine hospitalist with Texas Health Physicians Group and leader of the National Advocacy subcommittee for the Family Medicine Executive Council in SHM. Residents trained in bigger university hospital systems where internal medicine (IM) residents do mostly inpatient – in addition to outpatient services – and family medicine (FM) residents do mostly outpatient – including pediatrics and ob/gyn clinics in addition to inpatient services – may believe that to be the case in other systems too, Dr. Chaudhry explained.

"When you go to community hospital residency programs, it's totally different," he said. "It all depends. If you have only family medicine residency in a community hospital, they tend to do all training of inpatient clinical medicine, as IM training would in any other program"

Dr. McCurry noted that there seems to be a persisting, mental assumption that, as a family medicine doctor, you're going to be practicing outpatient only or maybe urgent care, which is historically just not the case. "If that's ingrained within the local hospital system, then it will be difficult for that system to hire a family medicine-trained hospitalist," she said.

Another source of outdated perceptions of family medicine come from hospital and institutional bylaws that have written internal medicine training in as a requirement for hospitalists. "In many bigger systems, and even in the smaller hospital community and regional hospitals, the bylaws of the hospitals were written approximately 20 years ago," Dr. Chaudhry said.

Unless someone has advocated for updating a hospital or institution's bylaws, they may have outdated requirements for hospitalists. "The situation right now is, in a lot of urban hospitals, they would be able to give a hospitalist position to internal medicine residents who just graduated, not even board certified, but they cannot give it to a hospitalist trained in family medicine who has worked for 10 years and is board certified, just because of the bylaws," said Dr. Odeti who is also co-chair for the SHM National Advocacy subcommittee of hospitalists trained in family medicine. "There is no good rhyme or reason to it. It is just there and they haven't changed it."

Dr. Chaudhry added that no one provides an adequate reason for the bias during the hiring process. "If you ask the recruiter, they would say 'the employer asked me [to do it this way].' If you ask the employers, they say 'the hospital's bylaws say that.' And then, we request changes to the hospital bylaws because you don't have access to them. So the burden of responsibility falls on the shoulders of hospitalists in leadership positions to request equal privileges from the hospital boards for FM-trained hospitalists."

Closing the gaps

Over the years, the American Board of Family Medicine and SHM have offered several opportunities for family medicine doctors to demonstrate their experience and training in hospital medicine. In 2010, ABFM began offering the Focused Recognition of Hospital Medicine board examination, together with the American Board of Internal Medicine. SHM also offers hospitalist fellowships and a designation of Fellow in Hospital Medicine (FHM) for health care professionals. In 2015, ABFM and SHM released a joint statement encouraging the growth of hospitalists trained in family medicine (HTFM) and outlining these opportunities.

These measures help fill a gap in both IM and FM training, but also appear to have some effect in convincing recruiters and employers to consider family medicine doctors for hospitalist positions. An abstract published at Hospital Medicine 2014 reviewed 252 hospitalist positions listed in journals and search engines attempted to document the disparities in job listings, the perceptions of physician recruiters, and how factors like experience, training,

and certification impacted a family medicine physician's likelihood to be considered for a position. HTFMs were explicitly mentioned as being eligible in 119 of 252 positions (47%). The investigators then sent surveys out to physician recruiters of the remaining 133 positions asking whether HTFMs were being considered for the position. The results of the survey showed 66% of the recruiters were open to HTFMs, while 34% of recruiters said they did not have a willingness to hire HTFMs.

That willingness to hire changed based on the level of experience, training, and certification. More than one-fourth (29%) of physician

Dr. Odeti

recruiters said institutional bylaws prevented hiring of HTFMs. If respondents earned a Recognition of Focused Practice in Hospital Medicine (RFPHM) board examination, 78% of physician recruiters would reconsider hiring the candidate. If the HTFM applicant had prior experience in hospital medicine, 87% of physician recruiters said they would consider the candidate. HTFMs who earned a Designation of Fellow in Hospital Medicine (FHM) from SHM would be reconsidered by 93% of physician recruiters who initially refused the HTFM candidate. All physician recruiters said they would reconsider if the candidate had a fellowship in hospital medicine.

However, to date, there is no official American College of Graduate Medical Education–recognized hospitalist board certification or designated specialty credentialing. This can lead to situations where family medicine–trained physicians are applying for jobs without the necessary requirements for the position, because those requirements may not be immediately obvious when first applying to a position. "There's often no specification until you apply and then are informed that you don't qualify – 'Oh, no, you haven't completed a fellowship,' or the added qualification in hospital medicine," Dr. McCurry said.

The 2015 joint statement from AAFP and SHM asserts that "more than two-thirds of HTFMs are also involved in the training of residents and medical students, enhancing the skills of our future physicians." But when HTFMs do find positions, they may be limited in other ways, such as being prohibited from serving on the faculty of internal medicine residency programs and teaching internal medicine residents. When Dr. Odeti was medical director for Johnston Memorial Hospital in Abingdon, Va., he said he encountered this issue.

"If you are a hospitalist who is internal medicine trained, then you can teach FM or IM, whereas if you're family medicine trained, you cannot teach internal medicine residents," he said. "What happened with me, I had to prioritize recruiting internal medicine residents over FM residents to be able to staff IM teaching faculty."

A rule change has been lobbied by SHM, under the direction of SHM family medicine SIG former chair David Goldstein, MD, to address this issue that would allow HTFMs with a FPHM designation to teach IM residents. The change was quietly made by the ACGME Review Committee for Internal Medicine in 2017, Dr. McCurry said, but implementation of the change has been slow.

"Essentially, the change was made in 2017 to allow for family medicine–trainied physicians who have the FPHM designation to teach IM residents, but this knowledge has not been widely dispersed or policies updated to clearly reflect this change," Dr. McCurry said. "It is a significant change, however, because prior to that, there were explicit policies preventing a family medicine hospitalist from teaching internal medicine residents even if they were experienced."

Using FM as an advantage

Requirements aside, it is "arguably not the case" that family medicine physicians need these extra certifications and fellowships to serve as hospitalists, Dr. McCurry said. It is difficult to quantify IM and FM hospitalist quality outcomes because of challenges with attribution, Dr. Odeti noted. One 2007 study published in the New England Journal of Medicine looked at patient quality and cost of care across the hospitalist model, and family medicine practitioners providing inpatients care. The investigators found similar outcomes in the internist model and with family practitioners providing inpatient care. Dr. Odeti said this research supports "the fact that family medicine physicians are equally competent as internists in providing inpatient care."

Dr. Odeti argued that family medicine training is valuable for work as a hospitalist. "Hospital medicine is a team sport. You have a quarterback, you have a wide receiver, you have a running back. Everybody has a role to play and everybody has their own strength," he said.

Family medicine hospitalists are uniquely positioned to handle the shift within hospital medicine from volume to value-based care. "That does not depend solely on what we do within the hospital. It depends a lot on what we do for the patients as they get out of the hospital into the community," he explained.

Family medicine hospitalists are also well prepared to handle the continuum of care for patients in the hospital. "In their training, FM hospitalists have their own patient panels and they have complete ownership of their patient in their training, so they are prepared because they know how to set up things for outpatients," Dr. Odeti explained.

"Every hospitalist group needs to use the family medicine doctors to their advantage," he said. "A family medicine–trained hospitalist should be part of every good hospitalist group, is what I would say."

Growing HTFMs within SHM

HTFMs are "all over," being represented in smaller hospitals, larger hospitals, and university hospitals in every state. "But to reach those positions, they probably have to go over more hurdles and have fewer opportunities," Dr. Chaudhry said.

There isn't a completely accurate count of family medicine hospitalists in the United States. Out of an estimated 50,000 U.S. hospitalists, about 16,000 hospitalists are members of SHM. A number of family medicine hospitalists may also take AAFP membership instead of SHM, Dr. Odeti explained.

However, there are a growing number of hospitalists within SHM with a family medicine background. In the 2007-2008 Society of Hospital Medicine Annual Survey, 3.7% of U.S. hospitalists claimed family medicine

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Obesity biggest risk for COVID-19 pneumonia, after age, male sex

By Marlene Busko

In a large international study of patients admitted to the ICU with COVID-19, the likelihood of having severe pneumonia (i.e., needing invasive mechanical ventilation) increased stepwise with increasing body mass index – independent of diabetes, hypertension, dyslipidemia, or current smoking.

The main finding was a linear correlation between BMI and need for invasive mechanical ventilation, after adjustment for center, age, sex, and other prespecified metabolic risk factors.

Risk was "highest for older people and males, but the next most important risk factor to developing severe pneumonia if infected [was] obesity," said François Pattou, MD,

Dr. Pattou

Centre Hospitalier Universitaire de Lille (France), who presented the findings at the ObesityWeek 2020 virtual meeting. The results were also recently published in a preprint article in The Lancet (2020. doi: 10.2139/ssrn.3667634).

Dr. Pattou and colleagues first reported back in April that obesity is one of the biggest risk factors for severe COVID-19 infection, especially in younger patients. Many further reports linked the two, and the French researchers then set out to conduct the current large, international, multicenter cohort study.

"The high number of patients included here [allowed us] to disentangle the role of various metabolic cofactors and to show that obesity, not diabetes or hypertension, was the main determinant of severe pneumonia [after age and gender]," Dr. Pattou said in an interview.

And the impact of obesity was most pronounced in women younger than 50 years.

Patients with severe obesity must protect themselves

Of interest, the study also found an "obesity paradox" for mortality after admission to the ICU.

Specifically, compared with leaner patients (BMI < 25 kg/m^2), those with severe obesity (obesity class III, BMI ≥ 40) had an increased risk of dying within 28 days of admission to ICU. But patients with overweight to moderate obesity (BMI 25-39.9) had a lower risk of this outcome.

"The second original finding of our study," Dr. Pattou continued, was the "nonlinear relation observed between BMI and all-cause mortality rate in ICU patients."

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training. That number increased to 6.9% of physicians who answered the SHM membership data report in 2010.

A Medscape Hospitalist Lifestyle, Happiness & Burnout Report from 2019 estimates 17% of hospitalists are trained in family medicine. In the 2020 *State of Hospital Medicine* Report, 38.6% of hospital medicine groups containing family medicine–trained physicians were part of a university, medical school, or faculty practice; 79.6% did not have academic status; 83.8% were at a nonteaching hospital; 60.7% were in a group in a nonteaching service at a teaching hospital; and 52.8% were in a group at a combination teaching/nonteaching service at a teaching hospital.

Although the Report did not specify whether family medicine hospitalists were mainly in rural or urban areas, "some of us do practice in underserved area hospitals where you have the smaller ICU model, critical access hospitals, potentially dealing with a whole gamut of inpatient medicine from ER, to the hospital inpatient adult cases, to critical care level," Dr. McCurry said. "But then, there are a large number of us who practice in private groups or at large hospitals, academic centers around the country," she added.

Recognition HTFM equally

The SHM family medicine SIG has been working to highlight the issue of hiring practices for HTFMs, and is taking a number of actions to bring greater awareness and recognition to family medicine hospitalists.

The family medicine SIG is looking at steps for requesting a new joint statement from ABFM and SHM focused on hiring practices for family medicine physicians as hospitalists. "I think it's worth considering now that we're at a point where we comprise about one-fifth of hospitalists as family medicine docs," Dr. McCurry said. "Is it time to take that joint statement to the next step, and seek a review of how we can improve the balance of hiring in terms of favoring more balanced consideration now that there are a lot more family medicine–trained hospitalists than historically?

"I think the call is really to help us all move to that next step in terms of identifying any of the lingering vestiges of expectation that are really no longer applicable to the hiring practices, or shouldn't be," she said.

The next step will be to ask hospitals with internal medicine–only requirements for hospitalists to update their bylaws to include family medicine physicians when considering candidates for hospitalist positions. If SHM does not make a distinction to grant Fellow in Hospital Medicine status between internal medicine– and family medicine–trained hospitalists, "then there should not be any distinction, or there should not be any hindrance by the recruiters, by the bigger systems, as well as by the employers" in hiring a family medicine–trained physician for a hospitalist position, Dr. Chaudhry said.

Dr. Odeti, who serves in several leadership roles within Ballad Health, describes the system as being friendly to HTFMs. About one-fourth of the hospitalists in Ballad Health are trained in family medicine. But when Dr. Odeti started his hospitalist practice, he was only one of a handful of HTFMs. He sees a future where the accomplishments and contributions of HTFMs will pave the way for future hospitalists. "Access into the urban hospitals is key, and I hope that SHM and the HTFM SIG will act as a catalyst for this change," he said.

> *"Truly, the best candidate for the position, regardless of background and training, is what you want. ... You want the best physician for your patients in the hospital."*

Colleagues of family medicine hospitalists, especially those in leadership positions at hospitals, can help by raising awareness, as can "those of our colleagues who sit on medical executive committees within their hospitals to review their bylaws, to see what the policies are, and encourage more competitiveness," Dr. McCurry said. "Truly, the best candidate for the position, regardless of background and training, is what you want. You want the best colleagues for your fellow hospitalists. You want the best physician for your patients in the hospital."

If training and all other things are equal, family medicine physicians should be evaluated on a case-by-case basis, she said. "I think that that puts the burden back on any good medical committee, and a good medical committee member who is an SHM member as well, to say, 'If we are committed to quality patient care, we want to encourage the recruitment of all physicians that are truly the best physicians to reduce that distinction between FM and IM in order to allow those best candidates to present, whether they are FM or IM.' That's all that we're asking."

Dr. Chaudhry emphasized that the preference for internal medicine–trained physicians isn't intentional. "It's not as if the systems are trying to do it," he said. "I think it is more like everybody needs to be educated. And through the platform of the Society of Hospital Medicine, I think we can make a difference. It will be a slow change, but we'll have to keep on working on it."

Dr. Odeti, Dr. McCurry, and Dr. Chaudhry have no relevant financial disclosures.

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Matteo Rottoli, MD, PhD, author of a related study, said the new trial "confirms the findings of our study, which are that obesity is an independent risk factor for intensive care admission and death."

Dr. Rottoli, from Alma Mater Studiorum, University of Bologna (Italy), and colleagues found that in their population of patients with COVID-19, a BMI > 35 was associated with a greater risk of death.

The takeaway message from the research is that "obesity should be considered one of the most important parameters to identify the population at risk," who should take extra precautions such as social distancing, Dr. Rottoli stressed.

Dr. Pattou agrees, particularly when it comes to severe obesity.

Intensive care physicians have learned a lot in the past months about COVID-19 pneumonia and how to address it (such as not precipitating intubation, using corticosteroids), he explained.

"Importantly, the general population has also learned a lot, and we can hope that patients with obesity, especially those with severe obesity, will take extra measures to protect themselves, resulting in a decrease of the incidence of severe pneumonia in young and severely obese patients," he added.

BMI distinct from other metabolic risk factors

Dr. Pattou said that, from Dec. 16, 2019, to Nov. 1, 2020, more than 45 million people worldwide tested positive for COVID-19 and more than 1.2 million people died from it.

Multiple studies have reported that, among people with COVID-19, those with obesity are at higher risk of hospitalization, ICU admission, invasive ventilation, and death, but it had not been clear if BMI was an independent risk factor.

Dr. Pattou and colleagues aimed to examine the relationship between BMI and COVID-19 pneumonia severity, defined by the need for mechanical ventilation (primary outcome), as well as 28-day all-cause mortality (secondary outcome) among patients admitted to the ICU.

They also sought to disentangle the effect of BMI from other metabolic risk factors (diabetes, hypertension, dyslipidemia, and current smoking) and examine the influence of age and sex on outcomes.

They performed a retrospective analysis of 1,461 patients with confirmed COVID-19 (positive reverse polymerase chain reaction test using a nasal or pharyngeal swab specimen) who were admitted to the ICU at 21 centers from Feb. 19 to May 11, 2020.

Participating centers were in France (13), Italy (3), the U.S. (1 in New York and 1 in Providence, R.I.), Israel (1), Belgium (1), and Spain (1).

Close to three-quarters of patients were men (73%), which is similar to multiple other studies, Dr. Pattou said. Patients were a mean age of 64 years and had a mean BMI of 28.1.

Half of patients had hypertension (52%), 29% had diabetes, 29% had hyperlipidemia, and 6.5% were current smokers.

Close to three-quarters (74%) required invasive mechanical ventilation, and 36% died within 28 days of ICU admission.

Each 5-kg/m^2 increase in BMI was associated with a 27% increased risk of mechanical ventilation in the overall cohort and a 65% increased risk of this outcome among women younger than 50 years, after adjustment for other risk factors.

Male sex and each 10-year increase in age were associated with an 82% and a 17% increased risk of ventilation, respectively, but hypertension, diabetes, hyperlipidemia, and current smoking were not associated with a greater risk. After adjustment for center, age, sex, and prespecified metabolic risk factors, obesity class III (BMI ≥ 40) was associated with a 68% increase in mortality, compared with the risk seen in lean patients.

The findings were similar across different centers.

"To our knowledge, this study represents the first international collaborative effort to explore the association of BMI with the outcomes of pneumonia among COVID-19 patients admitted to ICU," said the investigators.

They conclude that "available evidence should foster more focused and effective interventions in COVID-19 patients with the highest risk of severe pneumonia, in order to reduce future strain on intensive care resources worldwide, and inform physio-pathological research to elucidate the mechanism of severe lung damage in COVID-19."

The study did not receive specific funding. The authors have reported no relevant financial relationships.

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In the Literature

Clinician reviews of HM-centric research

By Ajay Bhasin, MD; Sophia Korovaichuk, MD; Cheryl Lee, MD; Tara Reddy, MD; Danielle Steker, MD; Katherine Welter, MD; David Young, MD

Division of Hospital Medicine, Northwestern University, Chicago

IN THIS ISSUE

By Ajay Bhasin, MD

1 Troponin elevation at any age is a risk for cardiac mortality

CLINICAL QUESTION: Is an elevated troponin value associated with increased mortality, regardless of age?

BACKGROUND: Although troponin is the preferred biomarker to indicate acute myocardial infarction, little is known about the implications of elevated troponin in the absence of plaque rupture.

STUDY DESIGN: Retrospective cohort study.

SETTING: Tertiary academic hospitals in the United Kingdom.

SYNOPSIS: The records of 257,948 hospitalized patients with a measured troponin value were analyzed over 8 years. Overall, a positive troponin conferred three times the mortality risk, with the strongest association in those aged 18-29 (hazard ratio, 10.6), compared with those aged 90 or older (HR, 1.5). It may be that those younger patients, for whom a troponin was ordered, are a fundamentally different, sicker cohort when compared with their peers and in contrast to the older patients for whom a troponin is widely sent. Furthermore, mortality increases with age, and a positive troponin may not impact the mortality rate as much as it does in a younger patient. Mortality was heavily concentrated in the first 3 months after discharge. The authors noted an inverted U-shaped relationship between troponin level and mortality in patients admitted to the hospital and in those with acute coronary syndrome. There was a direct positive correlation between troponin value and mortality until a certain threshold was crossed, at which point mortality decreased abruptly. This mortality drop off may result from a higher troponin leading to an increased likelihood of catheterization, a procedure that improves outcomes. Because of this study's retrospective nature, one cannot establish a causal relationship between troponin values and mortality. However, it highlights the need to study the mechanism for these outcomes across the age spectrum and to ensure close monitoring of elevated troponin values on an outpatient basis.

Dr. Bhasin

BOTTOM LINE: Elevated troponin levels are associated with an increased risk of mortality in all age groups and require close outpatient follow-up.

CITATION: Kaura A et al. Association of troponin level and age with mortality in 250,000 patients: Cohort study across five UK acute care centres. BMJ. 2019;367:I6055. doi: 10.1136/bmj.l6055.

Dr. Bhasin is a hospitalist at Northwestern Memorial Hospital and Lurie Children's Hospital and assistant professor of medicine, Feinberg School of Medicine, all in Chicago.

By Sophia Korovaichuk, MD

2 Comparing pulmonary embolism mortality risk scores

CLINICAL QUESTION: How well do risk scores estimate mortality outcomes in patients with acute pulmonary embolism (PE)?

BACKGROUND: Though most PEs do not have significant complications, 15% may be associated with risk of death or hemodynamic compromise. Retrospectively derived risk scores are used to risk-stratify patients and guide acute treatment strategies. It is unclear how well existing risk scores estimate mortality outcomes in patients with acute PE.

Dr. Korovaichuk

STUDY DESIGN: Multicenter cohort study.

SETTING: Eight hospitals participating in Pulmonary Embolism Response Team (PERT) consortium registry.

SYNOPSIS: The study included 416 patients with radiographically confirmed acute PE, baseline data for risk calculations, and PERT consultation to consider advanced therapies. Four risk scores (PESI, simplified PESI, BOVA, and European Society of Cardiology) were calculated for each patient independently of clinical care. Patients were assigned into lower- and higher-risk groups. All-cause mortality was assessed on days 7 and 30. The discrimination of each risk score was measured using area under the curve (AUC). Seven-day mortality ranged 1.3%-3.1% in the lower-risk group, and 7%-16.3% in the high-risk group. Thirty-day mortality in the low-risk group ranged 2.6%-10.2% and 14.4%-26.3% in the high-risk group. PE risk scores have only moderate discrimination for mortality at 7 days (AUC range, 0.616-0.666) and less discrimination at 30 days (AUC range, 0.550-0.694) with little association among the risk scores. Limitations include failure to capture all presenting PEs and inability to differentiate between all-cause and specific PE-related mortality.

BOTTOM LINE: While helpful in predicting shorter-term mortality, acute PE risk scores are not highly accurate at predicting longer-term mortality and should be integrated with broad clinical information when making management decisions.

CITATION: Barnes GD et al. Comparison of 4 acute pulmonary embolism mortality risk scores in patients evaluated by pulmonary embolism response teams. JAMA Netw Open. 2020 Aug 3;3(8):e2010779. doi: 10.1001/jamanetworkopen.2020.10779.

3 Early rhythm control in atrial fibrillation (EAST-AFNET trial)

CLINICAL QUESTION: Is rhythm control superior to rate control in treating early atrial fibrillation (AFib)?

BACKGROUND: Despite advances in AFib management, up to 5% of patients will have a major complication each year. Current guidelines favor rate control based on prior studies that did not show mortality benefit with rhythm control. By expanding the rhythm strategy to include catheter ablation in early AFib, this trial re-examines if implementing rhythm control leads to improved clinical outcomes.

STUDY DESIGN: Prospective, open blinded randomized controlled trial.

SETTING: 135 centers in 11 European countries.

SYNOPSIS: Of patients with a new AFib diagnosis (less than 1 year, median 36 days), 2,789 were randomized 1:1 to rhythm control or usual care. Patients were 75 years old or older with prior CVA or 2 or fewer cardiovascular conditions. Both arms were continued on guideline-directed treatment, including rate control medications and anticoagulation. Rhythm control involved use of antiarrhythmics, catheter ablation (8% at enrollment, 20% by 5 years), or early cardioversion. Patients assigned to rhythm control had a lower risk for primary composite outcome of CV death, stroke, or

hospitalization for worsening heart failure or acute coronary syndrome (HR, 0.79; 96% confidence interval, 0.66-0.94; *P* = .005) at 5 years, and the trial was stopped early for efficacy. Despite the 21% relative risk reduction, the absolute risk reduction was modest at 1.1 per 100 person-years. There were no significant differences in composite rate of all-cause mortality, although more adverse events occurred in the rhythm arm (4.9% vs. 1%). Overall rates of stroke and death were relatively low in both groups, underscoring the importance of continuing guideline-directed therapy. Hospital days were similar between the two groups, suggesting that rhythm control is not associated with higher cost burden. Limitations include its open-label design, loss of patients to follow-up (9% in control arm), and lack of generalizability to patients with long-standing AFib.

BOTTOM LINE: Early initiation of rhythm control therapy was associated with improved outcomes in patients with newly diagnosed AFib compared with usual care alone.

CITATION: Kirchhof P et al. Early rhythm-control therapy in patients with atrial fibrillation. N Engl J Med. 2020 Aug 29;383:1305-1316. doi: 10.1056/NEJMoa2019422.

Dr. Korovaichuk is a hospitalist at Northwestern Memorial Hospital and assistant professor of medicine, Feinberg School of Medicine, both in Chicago.

SHORT TAKES

Nasal MRSA screening can de-escalate anti-MRSA therapy

This retrospective cohort study evaluated MRSA nasal screening by isolating MRSA from cultures in a variety of locations. It demonstrated that the negative predictive value of a nasal MRSA nares screen is 96.5%, compared with blood culture completed within 7 days of the swab. Similar rates were found for both respiratory, wound, and urinary cultures. A negative nasal MRSA polymerase chain reaction may be sufficient to justify rapid de-escalation of anti-MRSA antibiotics, with allowance for clinical judgment. However, the positive predictive value of a nasal MRSA polymerase chain reaction was low and should not be used to justify empiric anti-MRSA antibiotics.

CITATION: Mergenhagen KA et al. Determining the utility of Methicillin-resistant *Staphylococcus aureus* nares screening in antimicrobial stewardship. Clin Infect Dis. 2020;71:1142-8. doi: 10.1093/cid/ciz974.

Third-generation cephalosporin remains appropriate treatment of spontaneous bacterial peritonitis

A multicenter retrospective study in Korea reviewed the charts of 865 patients hospitalized with their first episode of spontaneous bacterial peritonitis. The findings support the current standard use of third-generation cephalosporin. However, in a subset of critically ill, liver-failure patients, there was a significant reduction of in-hospital mortality with the use of carbapenem.

CITATION: Kim SW et al. Empirical treatment with carbapenem vs. third-generation cephalosporin for treatment of spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol. 2020 Jul 2:S1542-3565(20)30909-5. doi: 10.1016/j.cgh.2020.06.046.

Early endoscopy within 6 hours was not beneficial for those at high risk for rebleeding and death from upper GI bleed.

By Cheryl Lee, MD

4 Timing of endoscopy for acute upper GI bleeding

CLINICAL QUESTION: In high-risk patients hospitalized with upper GI bleeding, is earlier endoscopy beneficial?

BACKGROUND: Prior studies have failed to show a benefit to earlier endoscopic intervention in acute GI bleeding. However, those studies were performed in all-comers without attention to the varying risk within the patient population.

STUDY DESIGN: Randomized controlled trial.

SETTING: Single center in Hong Kong.

SYNOPSIS: Patients at high risk for further bleeding or death by clinical score were randomized to endoscopy within 6 hours ("urgent endoscopy"), vs. the following day ("early endoscopy"), of GI consultation. Those who required immediate endoscopic intervention because of hemodynamic instability were excluded. All were prescribed proton-pump inhibitor drip, with the addition of vasoactive drugs and antibiotics if there was a suspected variceal bleed. There was no difference in 30-day mortality between the two groups – 8.9% with urgent endoscopy and 6.6% with early endoscopy (HR, 1.35; 95% CI, 0.72-2.54). There was no difference in length of hospital stay or the number of transfusions. Earlier endoscopy within 6 hours was associated with a higher number of actively bleeding lesions requiring intervention and a nonstatistical increase in recurrent bleeding within 30 days. It is believed that more time on proton-pump inhibitor infusion prior to endoscopy allows for stabilization of bleeds, thus requiring less intervention when endoscopy does occur.

Dr. Lee

BOTTOM LINE: Early endoscopy within 6 hours was not beneficial for those at high risk for rebleeding and death from upper GI bleed.

CITATION: Lau JYW et al. Timing of endoscopy for acute upper gastrointestinal bleeding. N Engl J Med. 2020;382:1299-308. doi:10.1056/NEJMoa1912484.

5 Timing of renal-replacement therapy for AKI in the ICU

CLINICAL QUESTION: Does earlier initiation of renal-replacement therapy (RRT) improve mortality in the ICU?

BACKGROUND: Acute kidney injury (AKI) in the ICU is associated with high mortality. It is hypothesized that earlier initiation of RRT may benefit patients by controlling fluid overload and reducing metabolic stress caused by electrolyte and acid-base imbalances. However, prior studies have been conflicting, with the IDEAL-ICU study (2018) demonstrating no improvement in 90-day mortality with early RRT in septic shock.

STUDY DESIGN: Open-label randomized controlled trial.

SETTING: 168 hospitals in 15 countries.

SYNOPSIS: Of ICU patients with severe AKI, 3,019 were randomized to either early or standard initiation of RRT. Early RRT was defined as occurring within 12 hours of eligibility; in the standard-therapy group, RRT was delayed until specifically indicated or if there was no improvement after 72 hours. Those needing immediate renal replacement or deemed likely to recover without need for RRT were excluded in order to study only those in whom ideal timing of dialysis was uncertain. There was no difference in 90-day mortality between the groups (43.9% vs. 43.7%; *P* = .92). Early initiation did not improve length of ICU stay, ventilator-free days, days out of the hospital, or quality of life. The early-initiation patients experienced more adverse events related to RRT and were more likely to have continued dependence on RRT at 90 days (10.4% vs. 6.0% in standard initiation). Of note, approximately 40% of those randomized to standard initiation never required RRT.

BOTTOM LINE: This large, multicenter, well-conducted trial demonstrates no benefit for early initiation of RRT in critically ill patients.

CITATION: STARRT-AKI investigators. Timing of initiation of renal-replacement therapy in acute kidney injury. N Engl J Med. 2020;383:240-51. doi: 10.1056/NEJMoa2000741.

Dr. Lee is a hospitalist at Northwestern Memorial Hospital and Lurie Children's Hospital and assistant professor of medicine, Feinberg School of Medicine, all in Chicago.

By Tara Reddy, MD

6 Is ERCP indicated in gallstone pancreatitis without cholangitis?

CLINICAL QUESTION: How necessary is endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy in acute gallstone pancreatitis?

BACKGROUND: The timing and need for ERCP in the setting of gallstone pancreatitis without acute cholangitis has been debated widely. Guidelines recommend urgent ERCP for patients with gallstone pancreatitis with concurrent cholangitis, severe cholestasis, or a visualized stone in the duct, but it is unclear if ERCP benefits those with gallstone pancreatitis without those clear indicators.

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STUDY DESIGN: Prospective randomized controlled superiority trial.
SETTING: 26 hospitals in the Netherlands.
SYNOPSIS: Of patients with severe gallstone pancreatitis without cholangitis, 232 were randomized 1:1 to undergo urgent ERCP with biliary sphincterotomy (less than 24 hours after presentation) or conservative therapy (analgesia, intravenous fluids, with selective ERCP for cholangitis or persistent cholestasis). The primary endpoint was a composite score of mortality or major complications within 6 months of randomization. There was no difference in the primary endpoint, which occurred in 38% of the urgent-ERCP group and 44% of the conservative-therapy group (P = .37). In a subgroup of patients with cholestasis suggestive of biliary obstruction, the primary endpoint occurred in 32% of the urgent-ERCP group and 42% in the conservative group (P = .18). Similar rates of adverse events were observed between both groups. Limitations included difficulty in diagnosis of cholangitis, moderate positive predictive value of scoring tools to isolate those with severe pancreatitis, and lack of endoscopic ultrasound to determine the presence of ductal stones or sludge.


Dr. Reddy

BOTTOM LINE: Conservative management was equal to ERCP with sphincterotomy in patients with severe gallstone pancreatitis without cholangitis, and ERCP may be best reserved for patients with persistent cholestasis or later-developed cholangitis.
CITATION: Schepers NJ et al. Urgent endoscopic retrograde cholangiopancreatography with sphincterotomy versus conservative treatment in predicted severe acute gallstone pancreatitis (APEC): A multicentre randomised controlled trial. Lancet. 2020;396:167-76. doi: 10.1016/S0140-6736(20)30539-0.

Dr. Reddy is a hospitalist at Northwestern Memorial Hospital and instructor of medicine, Feinberg School of Medicine, both in Chicago.

In treatment of hyponatremia caused by SIADH, there was no benefit to adding furosemide with or without NaCl supplementation to fluid restriction.

By Danielle Steker, MD

7 Oakland score identifies patients with lower GI bleed at low risk for adverse events

CLINICAL QUESTION: Is the Oakland score a valid tool to assess the risk of adverse outcomes in adult patients with acute lower GI bleed (LGIB)?
BACKGROUND: The Oakland score was initially designed to be used in patients presenting with LGIB in the urgent, emergent, or primary care setting to help predict risk of readmission and determine if outpatient management is feasible. National guidelines in the United Kingdom have recommended use of the Oakland score despite limited external validation for the triage of patients with acute LGIB. This study aimed to externally validate the Oakland score in a large population in the United States and compare the performance at two thresholds.


Dr. Steker

STUDY DESIGN: Retrospective observational study.
SETTING: 140 hospitals across the United States.
SYNOPSIS: In this prognostic study, 38,067 patients were identified retrospectively using ICD-10 codes that were consistent with a diagnosis of LGIB and were admitted to the hospital. The Oakland score consisted of seven variables, including age, sex, prior hospitalization with LGIB, digital rectal exam results, heart rate, systolic blood pressure, and hemoglobin concentration. The primary outcome was safe discharge from the hospital, defined as absence of in-hospital rebleeding, RBC transfusion, therapeutic colonoscopy, mesenteric embolization or laparotomy for bleeding, in-hospital death, or readmission with subsequent LGIB in 28 days. In total, 47.9% of the identified patients experienced no adverse outcomes and were classified as meeting criteria for safe discharge. In addition, 8.7% of patients scored 8 points or fewer with a sensitivity of 98.4% and specificity of 16.0% for safe discharge. A sensitivity of 96% was maintained after increasing the threshold to 10 points or fewer with a specificity of 31.9%, suggesting the threshold can be increased while still maintaining adequate sensitivity. The study suggests that, by using the Oakland score threshold of 8, hospital admission may be avoided in low-risk patients leading to a savings of at least $44.5 million and even more if the threshold is increased to 10. Low specificity does present limitation of the score as some patients considered to be at risk for adverse events may have been safely discharged and managed as an outpatient, avoiding hospitalization.
BOTTOM LINE: The Oakland score was externally validated for use in assessing risk of adverse outcomes in patients with LGIB and had a high sensitivity but low specificity for identifying low-risk patients.
CITATION: Oakland K et al. External validation of the Oakland score to assess safe hospital discharge among adult patients with acute lower gastrointestinal bleeding in the US. JAMA Netw Open. 2020 Jul 1;3:e209630. doi: 10.1001/jamanetworkopen.2020.9630.

Dr. Steker is a hospitalist at Northwestern Memorial Hospital and instructor of medicine, Feinberg School of Medicine, both in Chicago.

By Katherine Welter, MD

8 Comparing the efficacy and safety of common SIADH treatments

CLINICAL QUESTION: Is fluid restriction or the addition of furosemide with or without NaCl supplementation more efficacious for the treatment of hyponatremia caused by syndrome of inappropriate antidiuretic hormone (SIADH)?
BACKGROUND: Hyponatremia caused by SIADH is common in hospitalized patients, and most evidence for treatment comes from noncontrolled studies. This study aims to investigate the efficacy and safety of fluid restriction compared with furosemide, with or without NaCl supplementation, for treating SIADH.
STUDY DESIGN: Open-label randomized controlled trial.
SETTING: Single center in Thailand.
SYNOPSIS: There were 92 participants randomized to fluid restriction alone, fluid restriction and furosemide, or fluid restriction, furosemide, and NaCl supplementation. The authors assessed the primary outcome, change in sodium,

at 4, 7, 14, and 28 days (baseline mean Na 125 mmol/L). By day 4, all groups had a significant increase in sodium (mean delta 5 mmol/L). The time to achieve a safe sodium level (Na less than 130 mmol/L) was not different among groups. Acute kidney injury was most common in patients who received furosemide and NaCl supplementation, compared with the fluid restriction and fluid restriction plus furosemide groups (32%, 10%, 17%, respectively; P = .07). Hypokalemia was also most common in the furosemide and NaCl group (42%, 13%, 23%, respectively; P = .01). Limitations include open-label study design, poor fluid restriction adherence (63% overall), and inflexible treatment regimens that excluded treatment with oral potassium.


Dr. Welter

BOTTOM LINE: In treatment of hyponatremia caused by SIADH, there was no benefit to adding furosemide with or without NaCl supplementation to fluid restriction. However, there was potential associated risk of acute kidney injury and hypokalemia.

CITATION: Krisanapan P et al. Efficacy of furosemide, oral sodium chloride, and fluid restriction for treatment of syndrome of inappropriate antidiuresis (SIADH): An open-label randomized controlled study (the EFFUSE-FLUID trial). Am J Kidney Dis. 2020 Aug;76(2):203-12. doi: 10.1053/j.ajkd.2019.11.012.

9 Intranasal vs. intramuscular naloxone in reversing opioid overdose

CLINICAL QUESTION: Is intranasal naloxone as effective as intramuscular naloxone in reversing opioid overdose at the same dose?

BACKGROUND: Naloxone is an opioid antagonist that works to treat opioid overdose. Few randomized trials have assessed the efficacy of intranasal administration, whereas more data have been published supporting use of intramuscular naloxone. This prospective trial examines the ability of the same dose (800 mcg per 1 mL solution) of intranasal naloxone vs. intramuscular naloxone at managing opioid overdose.

STUDY DESIGN: Double-blind double-dummy randomized clinical trial.

SETTING: Single supervised injection center in Sydney.

SYNOPSIS: In this study, 197 participants with opioid overdose were randomized to intramuscular or intranasal naloxone. If the patient did not respond to either (GSC score less than 13, RR less than 10, or oxygen saturation less than 95%), a rescue dose of intramuscular naloxone was given. Participants who received the intramuscular naloxone were less likely to need the rescue dose (8.6% vs. 23.1%; odds ratio, 0.35; *P* = .002). The time to achieve an RR greater than 10 (15 vs. 8 minutes) and GSC score greater than 13 (17 vs. 8 minutes) was longer in the intranasal than the intramuscular group. Limitations include the setting of a controlled environment. Also, this protocol called for an initial 5 minutes of ventilation prior to randomization, which selected for more severe overdose cases in the overall study population. More studies are needed to assess efficacy in the field, needlestick injuries, and larger intranasal doses.

BOTTOM LINE: Intranasal naloxone effectively reverses opioid overdose but not as effectively as intramuscular naloxone at the same dose.

CITATION: Dietze P et al. Effect of intranasal vs intramuscular naloxone on opioid overdose: A randomized clinical trial. JAMA Netw Open. 2019;2:e1914977. doi: 10.1001/jamanetworkopen.2019.14977.

Dr. Welter is a hospitalist at Northwestern Memorial Hospital and instructor of medicine, Feinberg School of Medicine, both in Chicago.

SHORT TAKES

PREDICT scoring tool quantifies the risk of infective endocarditis with *S. aureus* bacteremia

In this prospective validation of the PREDICT scoring tool, no patient with a score less than 2 on day 1 and day 5 developed endocarditis, which potentially identifies patients who may not need transesophageal echocardiogram. Surgery or invasive procedure in the prior 30 days, presence of prosthetic heart valve or heart failure, shorter time to positive blood culture, and increased percentage of bottles positive on the first culture were associated with higher risk of infective endocarditis and may have further predictive potential. The study was limited by the low number of patients with history of intravenous drug use, and further research is needed for external validation.

CITATION: Abu Saleh O et al. Prospective validation of PREDICT and its impact on the transesophageal echocardiography use in management of *Staphylococcus aureus* bacteremia. Clin Infect Dis. 2020 Jun 22. doi: 10.1093/cid/ciaa844.

Short courses of antibiotics may suffice for catheter-related GNR bacteremia

A single-center, retrospective, observational study of 54 patients showed, following catheter removal, equivalent rates of therapeutic failure between catheter-related Gram-negative rod bacteremia treated with antibiotic courses of 7 days or less, vs. courses greater than 7 days. This small study thus raises the question if shorter antibiotic courses may be sufficient for the treatment of Gram-negative rod catheter-related bloodstream infections.

CITATION: Ruiz-Ruigómez M et al. Impact of duration of antibiotic therapy in central venous catheter-related bloodstream infection due to Gram-negative bacilli. J Antimicrob Chemother. 2020 Jun 26;35(10):3049-55. doi: 10.1093/jac/dkaa244.

Cardiac consultation should be considered for those with prior stents; high-risk conditions, including acute coronary syndrome, severe valvular disease, or active heart failure, among other conditions; or high-risk findings on cardiovascular testing.

By David Young, MD

10 Optimizing perioperative cardiac risk assessment and management for noncardiac surgery

CLINICAL QUESTION: What is the sum of evidence supporting perioperative cardiac risk assessment and risk reduction?

BACKGROUND: There are extensive publications regarding preoperative risk assessment and optimization of risk management. This article is a review of current aggregate data from various meta-analyses and observational studies. It explores a systematic approach to preoperative risk assessment.

STUDY DESIGN: Literature review of meta-analyses and observational studies.

SETTING: A review of the current literature available in the MEDLINE database and Cochrane Library from 1949 to January 2020, favoring meta-analyses and clinical practice guidelines.

SYNOPSIS: A total of 92 publications were included in this review, which found history, physical exam, and functional capacity to be the best assessments of cardiac risk and should guide further preoperative management. Cardiovascular testing is rarely indicated except in those with clinical signs and symptoms of active cardiac conditions or with poor functional status undergoing high-risk surgery. Cardiac consultation should be considered for those with prior stents; high-risk conditions, including acute coronary syndrome, severe valvular disease, or active heart failure, among other conditions; or high-risk findings on cardiovascular testing. Preoperative medications should be individualized to patient-specific conditions. This study is limited by current available evidence and expert opinion, and the systematic approach suggested here has not been prospectively tested.


Dr. Young

BOTTOM LINE: Preoperative risk assessment and management should be largely based on individualized history, physical exam, and functional status. Cardiovascular work-up should be pursued only if it would influence surgical decision-making and perioperative care.

CITATION: Smilowitz NR, Berger JS. Perioperative cardiovascular risk assessment and management for noncardiac surgery: A review. JAMA. 2020 Jul 21;324:279-90. doi: 10.1001/jama.2020.7840.

Dr. Young is a hospitalist at Northwestern Memorial Hospital and instructor of medicine, Feinberg School of Medicine, both in Chicago.

HF an added risk in COVID-19, regardless of ejection fraction

By Patrice Wendling

People with a history of heart failure – no matter the type – face more complications and death than their peers without HF once hospitalized with COVID-19, a new observational study shows.

A history of HF was associated with a near doubling risk of in-hospital mortality and ICU care and more than a tripling risk of mechanical ventilation despite adjustment for 18 factors including race, obesity, diabetes, previous treatment with renin-angiotensin-aldosterone system (RAAS) inhibitors, and severity of illness.

Adverse outcomes were high regardless of whether patients had HF with a preserved, mid-range, or reduced left ventricular ejection fraction (HFpEF/HFmrEF/HFrEF).

"That for me was the real zinger," senior author Anuradha Lala, MD, said in an interview. "Because as clinicians, oftentimes, and wrongly so, we think this person has preserved ejection fraction, so they're not needing my heart failure expertise as much as someone with heart failure with reduced ejection fraction."

In the peak of the pandemic, that may have meant triaging patients with HFpEF to a regular floor, whereas those with HFrEF were seen by the specialist team.

"What this alerted me to is to take heart failure as a diagnosis very seriously, regardless of ejection fraction, and that is very much in line with all of the emerging data about heart failure with preserved ejection fraction," said Dr. Lala, an assistant professor of cardiology, population health science, and policy at the Icahn School of Medicine at Mount Sinai, New York.

"Now when I see patients in the clinic, I incorporate part of our visit to talking about what they are doing to prevent COVID, which I really wasn't doing before. It was like 'Oh yeah, what crazy times we're dealing with' and then addressing their heart failure as I normally would," she said. "But now, interwoven into every visit is: Are you wearing a mask, what's your social distancing policy, who are you living with at home, has anyone at home or who you've interacted with been sick? I'm asking those questions just as a knee-jerk reaction for these patients because I know the repercussions. We have to keep in mind these are observational studies, so I can't prove causality but these are observations that are, nonetheless, quite robust."

Although cardiovascular disease, including HF, is recognized as a risk factor for worse outcomes in COVID-19 patients, data are sparse on the clinical course and prognosis of patients with preexisting HF.

"I would have expected that there would have been a gradation of risk from the people with very low ejection fractions up into the normal range, but here it didn't seem to matter at all. So that's an important point that bad outcomes were independent of ejection fraction," commented Lee Goldberg, MD, professor of medicine and chief of advanced heart failure and cardiac transplant at the University of Pennsylvania, Philadelphia.

> *"As clinicians, if we see a patient presenting with COVID who has a history of heart failure we may want to be much more vigilant with that individual than we might otherwise be."*

The study also validated that there is no association between use of RAAS inhibitors and bad outcomes in patients with COVID-19, he said.

Although this has been demonstrated in several studies, concerns were raised early in the pandemic that ACE inhibitors and angiotensin receptor blockers could facilitate infection with SARS-CoV-2 and increase the risk of severe or lethal COVID-19.

"For most clinicians that question has been put to bed, but we're still getting patients that will ask during office visits 'Is it safe for me to stay on?' They still have that doubt [about] 'Are we doing the right thing?'" Dr. Goldberg said.

"We can reassure them now. A lot of us are able to say there's nothing to that, we're very clear about this, stay on the meds. If anything, there's data that suggest actually it may be better to be on an ACE inhibitor; that the hospitalizations were shorter and the outcomes were a little bit better."

For the current study, published online Oct. 28 in the Journal of the American College of Cardiology, the investigators analyzed 6,439 patients admitted for COVID-19 at one of five Mount Sinai Health System hospitals in New York between Feb. 27 and June 26. Their mean age was 65.3 years, 45% were women, and one-third were treated with RAAS inhibitors before admission.

With use of ICD-9/10 codes and individual chart review, HF was identified in 422 patients (6.6%), of which 250 patients had HFpEF (≥50%), 44 had HFmrEF (41%-49%), and 128 had HFrEF (≤40%).

Patients with HFpEF were older, more frequently women with a higher body mass index and history of lung disease than patients with HFrEF, whereas those with HFmrEF fell in between.

The HFpEF group was also treated with hydroxychloroquine or macrolides and noninvasive ventilation more frequently than the other two groups, whereas antiplatelet and neurohormonal therapies were more common in the HFrEF group.

Patients with a history of HF had significantly longer hospital stays than those without HF (8 days vs. 6 days), increased need for intubation (22.8% vs. 11.9%) and ICU care (23.2% vs. 16.6%), and worse in-hospital mortality (40% vs. 24.9%).

After multivariable regression adjustment, HF persisted as an independent risk factor for ICU care (odds ratio, 1.71; 95% confidence interval, 1.25-2.34), intubation and mechanical ventilation (OR, 3.64; 95% CI, 2.56-5.16), and in-hospital mortality (OR, 1.88; 95% CI, 1.27-2.78).

"I knew to expect higher rates of adverse outcomes but I didn't expect it to be nearly a twofold increase," Dr. Lala said. "I thought that was pretty powerful."

No significant differences were seen across EF categories in length of stay, need for ICU care, intubation and mechanical ventilation, acute kidney injury, shock, thromboembolic events, arrhythmias, or 30-day readmission rates.

However, cardiogenic shock (7.8% vs. 2.3% vs. 2%) and HF-related causes for 30-day readmissions (47.1% vs. 0% vs. 8.6%) were significantly higher in patients with HFrEF than in those with HFmrEF or HFpEF.

Also, mortality was lower in those with HFmrEF (22.7%) than with HFrEF (38.3%) and HFpEF (44%). The group was small but the "results suggested that patients with HFmrEF could have a better prognosis, because they can represent a distinct and more favorable HF phenotype," the authors wrote.

The statistical testing didn't show much difference and the patient numbers were very small, noted Dr. Goldberg. "So they might be overreaching a little bit there."

"To me, the take-home message is that just having the phenotype of heart failure, regardless of EF, is associated with bad outcomes and we need to be vigilant on two fronts," he said. "We really need to be doing prevention in the folks with heart failure because if they get COVID their outcomes are not going to be as good. Second, as clinicians, if we see a patient presenting with COVID who has a history of heart failure we may want to be much more vigilant with that individual than we might otherwise be. So I think there's something to be said for kind of risk-stratifying people in that way."

Dr. Goldberg pointed out that the study had many "amazing strengths," including a large, racially diverse population, direct chart review to identify heart failure patients, and capturing a patient's specific HF phenotype.

Weaknesses of the study are that it was a single-center analysis, so the biases of how these patients were treated are not easily controlled for, he said. "We also don't know when the hospital system was very strained as they were making some decisions: Were the older patients who had advanced heart and lung disease ultimately less aggressively treated because they felt they wouldn't survive?"

Dr. Lala has received personal fees from Zoll, outside the submitted work. Dr. Goldberg reported research funding with Respicardia and consulting fees from Abbott.

A version of this article originally appeared on Medscape.com.

About 17% of COVID-19 survivors retest positive in follow-up study

By Damian McNamara

For reasons unknown, about one in six people who recovered from COVID-19 subsequently retested positive at least 2 weeks later, researchers reported in a study in Italy.

Sore throat and rhinitis were the only symptoms associated with a positive result. "Patients who continued to have respiratory symptoms, especially, were more likely to have a new positive test result," lead author Francesco Landi, MD, PhD, said in an interview

"This suggests the persistence of respiratory symptoms should not be underestimated and should be adequately assessed in all patients considered recovered from COVID-19," he said.

"The study results are interesting," Akiko Iwasaki, PhD, an immunobiologist at Yale University and the Howard Hughes Medical Institute, both in New Haven, Conn., said in an interview. "There are other reports of RNA detection post discharge, but this study ... found that only two symptoms out of many – sore throat and rhinitis – were higher in those with PCR [polymerase chain reaction]-positive status."

The study was published online Sept. 18 in the American Journal of Preventive Medicine (doi: 10.1016/j.amepre.2020.08.014).

The findings could carry important implications for people who continue to be symptomatic. "It is reasonable to be cautious and avoid close contact with others, wear a face mask, and possibly undergo an additional nasopharyngeal swab," said Dr. Landi, associate professor of internal medicine at Catholic University of the Sacred Heart in Rome.

"One of most interesting findings is that persistent symptoms do not correlate with PCR positivity, suggesting that symptoms are in many cases not due to ongoing viral replication," Jonathan Karn, PhD, professor and chair of the department of molecular biology and microbiology at Case Western Reserve University, Cleveland, said in an interview.

"The key technical problem, which they have discussed, is that a viral RNA signal in the PCR assay does not necessarily mean that infectious virus is present," Dr. Karn said. He added that new comprehensive viral RNA analyses would be needed to answer this question.

Official COVID-19 recovery

To identify risk factors and COVID-19 survivors more likely to retest positive, Dr. Landi and members of the Gemelli Against COVID-19 Post-Acute Care Study Group evaluated 131 people after hospital discharge.

All participants met World Health Organization criteria for release from isolation, including two negative test results at least 24 hours apart, and were studied between April 21 and May 21. Mean age was 56 and 39% were women. Only a slightly higher mean body mass index of 27.6 kg/m^2 in the positive group versus 25.9 in the negative group, was significant.

Although 51% of survivors reported fatigue, 44% had dyspnea, and 17% were coughing, the rates did not differ significantly between groups. In contrast, 18% of positive survivors and 4% of negative survivors had a sore throat (P = .04), and 27% versus 12%, respectively, reported rhinitis (P = .05).

People returned for follow-up visits a mean 17 days after the second negative swab test.

Asymptomatic carriers

"These findings indicate that a noteworthy rate of recovered patients with COVID-19 could still be asymptomatic carriers of the virus," the researchers noted in the paper. "Even in the absence of specific guidelines, the 22 patients who tested positive for COVID-19 again were suggested to quarantine for a second time."

No family member or close contact of the positive survivors reported SARS-CoV-2 infection. All patients continued to wear masks and observe social distancing recommendations, which makes it "very difficult to affirm whether these patients were really contagious," the researchers noted.

Next steps

Evaluating all COVID-19 survivors to identify any who retest positive "will be a crucial contribution to a better understanding of both the natural history of COVID-19 as well as the public health implications of viral shedding," the authors wrote.

One study limitation is that the reverse transcriptase–PCR test reveals genetic sequences specific to COVID-19. "It is important to underline that this is not a viral culture and cannot determine whether the virus is viable and transmissible," the researchers noted.

"In this respect, we are trying to better understand if the persistence of long-time positive [reverse transcriptase]–PCR test for COVID-19 is really correlated to a potential contagiousness," they added.

Dr. Landi and colleagues said their findings should be considered preliminary, and larger data samples are warranted to validate the results.

Dr. Landi and Dr. Karn disclosed no relevant financial relationships. Dr. Iwasaki disclosed a research grant from Condair, a 5% or greater equity interest in RIGImmune, and income of $250 or more from PureTec.

A version of this article originally appeared on Medscape.com.

U.S. Air Force photo by Senior Airman Pedro Tenorio

Reducing admissions for alcohol withdrawal syndrome

Hospitalists can drive major changes with a QI project

Hospitalists in the VA system see patients with symptoms of alcohol withdrawal frequently – there are about 33,000 hospital admissions each year for alcohol withdrawal syndrome (AWS), says Robert Patrick, MD, of the Louis Stokes Cleveland VA Medical Center.

"By contrast, the number of admissions for the largest ambulatory care sensitive condition (heart failure) is only about 28,000," he said. "If alcohol detox were an ambulatory care sensitive condition, it would be the largest in the VA by a substantial margin."

The purpose of the project he and his coauthor, Laura Brown, MD, created to address the problem was to increase the number of patients treated for AWS as outpatients and decrease hospital admissions – without increasing readmissions or clinical deterioration.

They introduced four core operational changes for their study:

1. Standardized risk stratification in the Emergency Department to identify low-risk patients for outpatient treatment.

2. Benzodiazepine-sparing symptom-triggered medication regimen.

3. Daily clinical dashboard surveillance and risk stratification for continued hospital stay.

4. Telephone follow-up for patients discharged from the ED or hospital.

With these changes in place, 8 months of data showed a 50% reduction in AWS admissions and a 40% reduction in length of stays.

Their conclusion? "A well-designed and -executed QI [quality improvement] project can dramatically reduce hospitalist workload, while at the same time improving patient safety," Dr. Patrick said. "Hospitalists just have to be willing to think outside the box, work with nursing and coordinate care outside of the hospital to make it happen."

He added a caveat for hospital medicine groups still in a fee-for-service environment. "This saves money for the payer, not the hospital," he said. "In our case they are one and the same, so the ROI [return on investment] is huge. If you are part of an ACO [accountable care organization] this is probably true for you, but I would check with your ACO first."

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Getting closer to an accurate early Alzheimer's test

Researchers have created the most sensitive test yet

ChrisChrisW/Getty Images

Scientists at Washington University in St. Louis have developed the most sensitive blood test yet for Alzheimer's. In studies, the test identified patients with amyloid deposits, using mass spectrometry, before brain scans did.

Of course, amyloid is a normal brain protein; most people with amyloid deposits will not develop dementia, but it's a significant risk factor. When blood amyloid levels are low, it may indicate it is clumping in the brain.

Researchers used mass spectrometry to test volunteers' stored blood for beta-amyloid, then checked if the levels predicted the results of PET scans. Mass spectrometry identified asymptomatic people accumulating beta-amyloid in their brains when PET scans were still negative. The scans showed beta amyloid in the brain only years later. The blood test predicted the presence of plaque even in mostly asymptomatic people with 94% accuracy.

The test will not be available for clinical use for years, but prior to that it will be helpful to scientists conducting trials of drugs to prevent Alzheimer's, seeking participants in the earliest stages of the disease.

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Quick Byte: Looking back

How quickly things change. On Sept. 23, 2019 – months before the COVID-19 pandemic struck – at a United Nations High-Level Meeting on Universal Health Coverage, heads of state from around the world pledged to achieve universal health coverage by 2030.

"This will be an unprecedented moment in public health: according to the declaration negotiated by member states, this commitment is being made globally 'for the first time.' Whether or not the new commitment succeeds will depend on a large degree of advocacy at the national level," as people will need to "demand more of their governments," the declaration notes.

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Getting to secure text messaging in health care

Hospitalists and health care teams struggle with issues related to text messaging in the workplace. "It's happening whether an institution has a secure text-messaging platform or not," said Philip Hagedorn, MD, MBI, associate chief medical information officer at Cincinnati Children's Hospital Medical Center.

"Many places reacted to this reality by procuring a solution – take your pick of secure text-messaging platforms – and implementing it, but bypassed an opportunity to think about how we tailor the use of this culturally ubiquitous medium to the health care setting," he said.

It doesn't work to just drop a secure text-messaging platform into clinical systems and expect that health care practitioners will know how to use them appropriately, Dr. Hagedorn says. "The way we use text messaging in our lives outside health care inevitably bleeds into how we use the medium at work, but it shouldn't. The needs are different and the stakes are higher for communication in the health care setting."

In a paper looking at the issue, Dr. Hagedorn and co-authors laid out critical areas of concern, such as text messaging becoming a form of alarm fatigue and also increasing the likelihood of communication error.

"It's my hope that fellow hospitalists can use this as an opportunity to think deeply about how we communicate in health care," he said. "If we don't think critically about how and where something like text messaging should be used in medicine, we risk facing unintended consequences for our patients."

The article discusses several steps for mitigating the risks laid out, including proactive surveillance and targeted training. "These are starting points, and I'm sure there are plenty of other creative solutions out there. We wanted to get the conversation going. We'd love to hear from others who face similar issues or have come up with interesting solutions."

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The University of Arkansas for Medical Sciences – Department of Internal Medicine is seeking BC/BE Hospitalist and Nocturnists

Hospitalist Opportunities

The University of Arkansas for Medical Sciences Department of Internal Medicine is seeking an Assistant Professor to serve the Department's Division of Hospital Medicine in Little Rock, AR. Candidate will teach medical students, residents, and fellows in the area of acute inpatient internal Medicine. Candidate will provide care directly to hospitalized inpatients. Candidate will have opportunity to perform quality improvement, overcomes research, and/or curriculum development related to impatient medicine.

Nocturnist Opportunities

The University of Arkansas for Medical Sciences Department of Internal Medicine is seeking nocturnists to serve the Department's Division of Hospital Medicine in Little Rock, AR. Candidate will provide care directly to hospitalized inpatients. Candidate will also have the opportunity to teach medical students and residents in the area of acute inpatient internal Medicine. This is an increased compensation position out of regard for the nocturnal timeframe.

Requirements include M.D. or equivalent, completion of residency program (3 years) in Internal Medicine and license to practice medicine or eligibility for licensure in Arkansas. Salary is commensurate with experience.

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Candidates must have a M.D. degree or equivalent. Applications will be accepted for positions at the rank of Associate, no track, or Clinical Assistant Professor, commensurate with experience and training. Position requires completion of an ACGME-accredited Residency Program.

Primary practice sites are the University of Iowa Hospitals and Clinics (UIHC), which is consistently recognized as one of the top health care employers by *Forbes* and has consistently ranked as one of the top 15 medical centers in the U.S. by *US News and World Report.* Iowa City is a diverse and family-friendly community located in the heart of the Midwest. As the site of the University of Iowa, it combines access to many of the cultural amenities of a larger city with the ease of living in a smaller town.

For further information, contact Evelyn Kinne at **evelyn-kinne@uiowa.edu**

Interested candidates are invited to search the Jobs@UIOWA site: **https://jobs.uiowa.edu/content/faculty/** and search for requisition # 73980

The University of Iowa is an equal opportunity/affirmative action employer. All qualified applicants are encouraged to apply and will receive consideration for employment free from discrimination on the basis of race, creed, color, national origin, age, sex, pregnancy, sexual orientation, gender identity, genetic information, religion, associational preference, status as a qualified individual with a disability, or status as a protected veteran. The University also affirms its commitment to providing equal opportunities and equal access to University facilities. Women and Minorities are encouraged to apply for all employment vacancies.

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- Up to $40K sign on bonus

Nocturnist or Traditional Hospitalist, Oconee Memorial Hospital

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- Up to $40K sign on bonus

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PHM FELLOWS

Flattening the hierarchy

What fellows can learn about leadership from aircraft crews

By Brandon Palmer, MD

Fellowship is a time of great growth for pediatric hospital medicine fellows as clinicians, educators, scholars, and as leaders. Leadership is a crucial skill for hospitalists that is cultivated throughout fellowship. As fellows, we step into the role of clinical team leader for the first time and it is our responsibility to create a clinical and educational environment that is safe, inviting and engaging.

For possibly the first time in our careers, pediatric hospital medicine fellows are expected to make final decisions, big and small. We are faced with high-pressure situations almost daily, whether it is a rapid response on a patient, tough diagnostic and therapeutic decisions, difficult conversations with families, or dealing with challenging team members.

Soon after starting fellowship I was faced with a such a situation. The patient was a 6-month-old infant with trisomy 21 who was admitted because of feeding difficulties. They were working on oral feeds but required nasogastric (NG) feeds to meet caloric needs. On my first day on service, the residents indicated that the medical team desired the patient to have a gastrostomy tube (G-tube) placed. I was hoping to send the patient home for a few weeks with the NG tube to see if they were making progress on their oral feeds before deciding on the need for a G-tube. However, the patient's parents pulled me aside in the hallway and said they were considering a third possibility.

The parents felt strongly about a trial period of a few weeks without the NG tube to see if the patient was able to maintain adequate weight gain with just oral feeds. The bedside nurse reiterated that the family felt their concerns had not been considered up until this point. As the fellow and team leader, it was my job to navigate between my resident team, myself, and the family in order to make a final decision. Through a bedside meeting and shared decision-making, we were able to compromise and negotiate a decision, allowing the patient to go home on just oral feeds with close follow-up with their pediatrician.

Afterward, I found myself searching for strategies to be a better leader in these situations.

I found a potential answer in a recent article from the Harvard Business Review titled "What Aircraft Crews Know About Managing High-Pressure Situations."[1] The article discusses crew resource management (CRM), which was developed in the 1980s and is used in aviation worldwide. CRM is based on two principles to improve crisis management: The hierarchy on the flight deck must be flattened, and crew members must be actively integrated into the flight's workflows and decision-making processes.

If we can model ourselves after the airline industry by following the principles of CRM, then we will be better clinicians, educators, and leaders.

The authors of the article conducted two different studies to further understand CRM and its effects. The first study included observing 11 flight crews in emergency simulations. In the study, the flight crew had to react to an emergency, and then conduct a landing of the aircraft. The authors found that the captain's style of communication had a major impact on crew performance in two major ways: Crews performed consistently better under times of pressure when the copilot was included in the decision-making process, and captains who asked open-ended questions came up with better solutions than captains who asked "yes or no" questions.

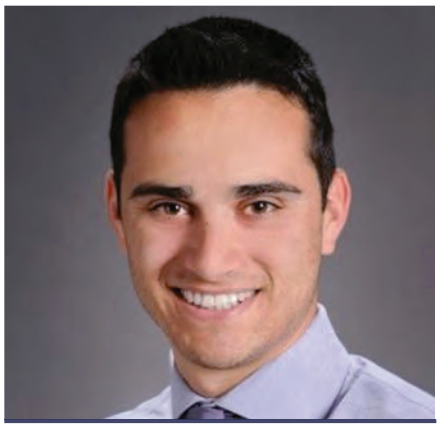
The authors conclude that "involving colleagues as equal decision partners by asking them questions … aids constructive, factual information exchange." The second study consisted of conducting 61 interviews with flight crew members to better understand crisis management. In the interviews, the same theme occurred, that open-ended questions are vital in all decision-making processes and may be preventative against dangerous or imperfect outcomes. As fellows and team leaders we can learn from CRM and these studies. We need to flatten the hierarchy and ask open-ended questions.

To flatten the hierarchy, we should value the thoughts and opinions of all our team members. Now more than ever in this current COVID-19 pandemic with many hospitals instituting telehealth/telerounding for some or all team members, it is essential to utilize our entire "flight crew" (physicians, nurses, therapists, subspecialists, social workers, case managers, etc.) during routine decisions and high-stake decisions. We should make sure our flight crew, especially the bedside nurse is part of the decision-making process.[2] This means we need to ensure they are present and given a voice on clinical rounds. To flatten the hierarchy, we must take pride in eliciting other team member's opinions. We must realize that we alone do not have all the answers, and other team members may have different frameworks in which they process a decision.

Finally, in medicine, our patients and families are included in our flight crew. They too must have a voice in the decision-making process. Previous studies have shown that patients and families desire to be included in the process, and opportunities exist to improve shared decision-making in pediatrics.[3-5] Lastly, we should commit to asking open-ended questions from our team and our patients. We should value their input and use their answers and frameworks to make the best decision for our patients.

I wasn't aware at the time, but I was using some of the principles of CRM while navigating my high-pressure situation. A bedside meeting with all team members and the patient's family helped to flatten the hierarchy by understanding and valuing each team member's input. Asking open-ended questions of the different team members led to a more inviting and engaging clinical and learning environment. These strategies helped to lead our team into a clinical decision that wasn't entirely clear at first but ended up being the best decision for the patient, as they are now thriving without ever requiring supplemental nutrition after discharge.

As physicians, we have learned a lot from the airline industry about wellness and the effect of fatigue on performance. We can also learn from them about clinical decision-making and leadership strategies. When adopted for health care, CRM principles have been shown to result in a culture of safety and long-term behavioral change.[6,7] If we can model ourselves after the airline industry by following the principles of CRM, then we will be better clinicians, educators, and leaders.



Dr. Palmer is a second-year pediatric hospital medicine fellow at Children's Hospital Los Angeles and is working toward a master's in academic medicine at the University of Southern California, Los Angeles, with a focus on curriculum development and educational scholarship production.

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Ferring is committed to exploring the crucial link between the gut microbiome and the threat of recurrent *Clostridioides difficile* infections. With the 2018 acquisition of Rebiotix and several other alliances, Ferring is rapidly advancing its microbiome research, developing novel therapies to address significant unmet needs in deadly and debilitating diseases, and helping people live better lives.

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