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The ally in the waiting room

Improving communication with patients' loved ones

By Eric Butterman

We think of a patient's recovery happening in multiple locations – in a hospital room or a rehabilitation facility, for example. But many clinicians may not consider the opportunity to aid healing that lies in the waiting room.

The waiting room is where a patient's loved ones often are, and they, sometimes more than anyone, can unlock the path to a patient's quicker recovery. Friends and family can offer encouragement, as they have an existing bond of trust that can help if a patient needs reinforcement to take their medications or follow other health care advice.

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COMMENTARY

Physicians, make a plan to vote

By Anika Kumar, MD, FHM, FAAP

Dr. Kumar is the pediatric editor of The Hospitalist. She is clinical assistant professor of pediatrics at the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University and a pediatric hospitalist at Cleveland Clinic Children's.

In March 2020, following the announcement of the United States' first death related to COVID-19, many physicians began using their voices to discuss the shortage of personal protective equipment (PPE). Many physicians, myself included, petitioned elected leaders at the community, state, and federal levels to address the PPE shortage.

Historically, physicians have advocated for improved public health. From seat belt laws in the 1980s and 1990s to the Affordable Care Act in the 2000s, physicians have testified at the community, state, and federal levels to advocate for the health and safety of our patients and the public. Yet while we have been making our voices heard, we are often silent at the ballot box.

In the 1996 and 2000 elections, physicians voted 9% less often than the general public, and compared with lawyers – professionals with similar educational attainment and finances – physicians voted 22% less often.[1] It is unclear why physicians are less likely to vote. In a 2016 article, David Grande, MD, and Katrina Armstrong, MD, postulated that physicians may not vote because our work hours create barriers to visiting polls.[2]

Despite our lack of engagement at the ballot box, voting is important to improving our patients' social determinants of health. In a recently published systematic review, the authors found several studies supporting the association between voting and social determinants of health. Their review found that, when large numbers of people from communities participated in voting, it translated into greater influence over determining who held political power in that community. Those with power introduced and supported policies responding to their constituents' needs, ultimately influencing their constituents' social determinants of health.[3] By voting, we as physicians are helping to address the social determinants of health in our communities.

Many medical students have been doing their part to improve the social determinants of health in their communities by pledging to vote. In 2018, the American Medical Student Association launched their "Med Out the Vote" initiative prior to the election. The organization called on all health care providers and providers in training to pledge to vote in the election.[4] They are continuing these efforts for the 2020 elections.

We should join our nation's medical students by also pledging to vote. To begin, we can all *Make A Plan To Vote*. Each plan should include the following:

- **Register to vote:** In many states eligible voters can register online.
- **Request an absentee ballot:** Many states require registered voters to request absentee ballots online or by mail.
- **Vote:** Submit an absentee ballot prior to election or vote in-person on election day. Some counties allow voting early in person.

In practice, our plans will differ slightly because each state has its own election laws.

This election season let us ensure all physician voices are heard. *Make A Plan To Vote* for your patients and communities.

References

1. Grande D et al. Do doctorsvote? J Gen Intern Med. 2007 May;22(5):585-9.
2. Grande D, Armstrong K. Will physicians vote? Ann Intern Med. 2016;165:814-5.
3. Brown CL et al. Voting, health and interventions in healthcare settings: A scoping review. Public Health Rev. 2020 Jul. doi: 10.1186/s40985-020-00133-6.
4. American Medical Student Association. AMSA launches Med Out the Vote campaign, call to action. 2018 Jul 29. Accessed 2020 Sep 14. https://www.amsa.org/about/amsa-press-room/amsa-launches-med-out-the-vote-campaign-call-to-action/.

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*BASED ON CLINICAL TRIAL DATA VS WARFARIN IN PATIENTS WITH NVAF.

Visit EliquisData.com

INDICATION

ELIQUIS is indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).

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.

ARISTOTLE study design[1,2]

A phase III, double-blind, randomized trial designed to compare the effects of ELIQUIS 5 mg twice daily* (n=9120) and warfarin (n=9081) (target INR range: 2.0-3.0) in reducing the risk of stroke and systemic embolism in 18,201 patients with NVAF and ≥1 additional risk factor for stroke: prior stroke or transient ischemic attack (TIA); prior systemic embolism; age ≥75 years; arterial hypertension requiring treatment; diabetes mellitus; heart failure ≥New York Heart Association (NYHA) Class 2; or left ventricular ejection fraction (LVEF) ≤40%. Patients were followed for a median of ≈1.7 years. The 2 treatment groups were well balanced with respect to baseline characteristics, including age, stroke risk at entry as measured by $CHADS_2$ score,† and prior vitamin K antagonist (VKA) experience. The primary efficacy endpoint was stroke/systemic embolism, and the primary safety endpoint was major bleeding. Patients who needed aspirin >165 mg/day or needed aspirin plus a thienopyridine (eg, clopidogrel) were excluded from ARISTOTLE.

AVERROES study design[1,3]

AVERROES was a phase III, double-blind, randomized trial designed to compare the effects of ELIQUIS 5 mg twice daily* (n=2807) and aspirin (81 mg–324 mg once daily) (n=2791) in reducing the risk of stroke and systemic embolism in 5598 patients with NVAF thought not to be candidates for warfarin therapy, and with ≥1 additional risk factor for stroke: prior stroke or TIA; age ≥75 years of age; arterial hypertension (receiving treatment); diabetes mellitus (receiving treatment); heart failure (≥NYHA Class 2 at the time of enrollment); LVEF ≤35%, or documented peripheral artery disease. Patients could not be receiving VKA therapy (eg, warfarin), either because it had already been demonstrated to be or was expected to be unsuitable for them. The 2 treatment groups were well balanced with respect to baseline characteristics, including age, stroke risk at entry as measured by $CHADS_2$ score,† and prior use of a VKA within 30 days before screening. The mean follow-up period was approximately 1.1 years. The primary efficacy endpoint was stroke/systemic embolism, and the primary safety endpoint was major bleeding.

*A dose of 2.5 mg twice daily was assigned to patients with at least 2 of the following characteristics: age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL.[1]
†Scale from 0 to 6 to estimate stroke risk; higher scores predict greater risk.[1]

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

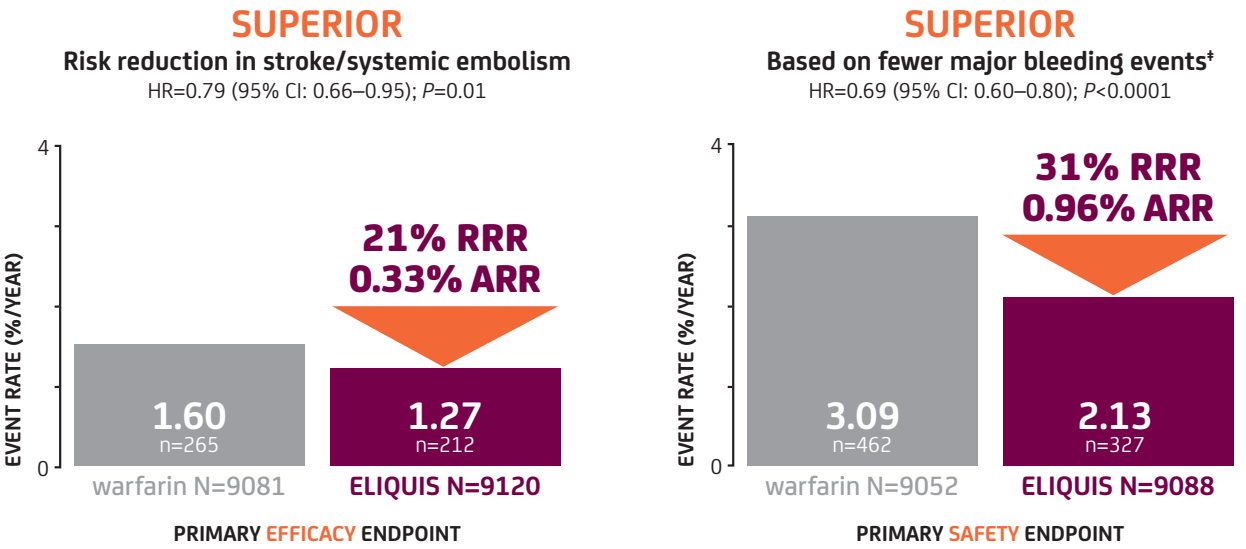
- **Combined P-gp and Strong CYP3A4 Inhibitors:** Inhibitors of P-glycoprotein (P-gp) and cytochrome P450 3A4 (CYP3A4) increase exposure to apixaban and increase the risk of bleeding. For patients receiving ELIQUIS doses of 5 mg or 10 mg twice daily, reduce the dose of ELIQUIS by 50% when ELIQUIS is 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 PATIENTS WITH NVAF

ARISTOTLE: ONLY ELIQUIS demonstrated superiority in BOTH stroke/systemic embolism and major bleeding vs warfarin[1]



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

- Superiority to warfarin was primarily attributable to a reduction in hemorrhagic stroke and ischemic strokes with hemorrhagic conversion compared to warfarin. Purely ischemic strokes occurred with similar rates on both drugs[1]
- In another clinical trial (AVERROES), ELIQUIS was associated with an increase in major bleeding compared with aspirin that was not statistically significant (1.41%/yr vs 0.92%/yr, HR=1.54 [95% CI: 0.96–2.45]; *P*=0.07)[1]
- The most common reason for treatment discontinuation in both ARISTOTLE and AVERROES was 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[1]

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

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.

‡Bleeding events were counted during treatment or within 2 days of stopping study treatment (on-treatment period). Bleeding events within each subcategory were counted once per subject, but subjects may have contributed events to multiple endpoints.[1]

§In AVERROES, a decrease in hemoglobin of 2 g/dL or more over a 24-hour period.[3]

¶In ARISTOTLE, intracranial bleeding included intracerebral, intraventricular, subdural, and subarachnoid bleeding. Any type of hemorrhagic stroke was adjudicated and counted as intracranial major bleeding.[1]

ARR=absolute risk reduction; CI=confidence interval; HR=hazard ratio; INR=international normalized ratio; 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.** Granger CB, Alexander JH, McMurray JJV, et al; for ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365(11):981-992. **3.** Connolly SJ, Eikelboom J, Joyner C, et al; for AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364(9):806-817.

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.

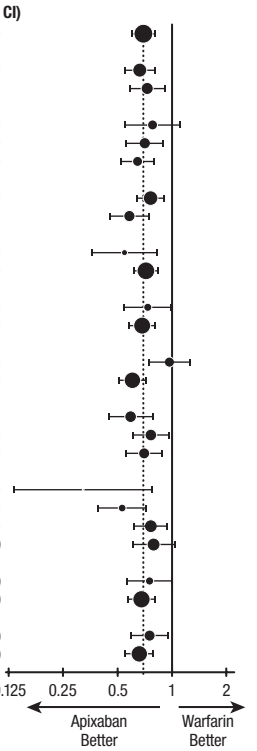
Table 3: Bleeding During the Treatment Period in Patients Undergoing Elective Hip or Knee Replacement Surgery

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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The Authority/Accountability balance

Evaluating your career trajectory

By Thomas McIlraith, MD, SFHM, CLHM

I have had the pleasure of working on the Society of Hospital Medicine's signature Leadership Academies since 2010, and I enjoy working with hospital medicine leaders from around the country every year. I started as a hospital medicine leader in 2000 and served during the unprecedented growth of the field when it was "the most rapidly growing specialty in the history of medicine."

Most businesses dream of having a year of double-digit growth; my department grew an average of 15% annually for more than 10 years. These unique experiences have taught me many lessons and afforded me the opportunity to watch many stars of hospital medicine rise, as well as to learn from several less-scrupulous leaders about the darker side of hospital politics.

One of the lessons I learned the hard way about hospital politics is striking the "Authority/Accountability balance" in your career. I shared this perspective at the SHM annual conference in 2018, at speaking engagements on the West Coast, and with my leadership group at the academies. I am sharing it with you because the feedback I have received has been very positive.

The Authority/Accountability balance is a tool for evaluating your current career trajectory and measuring if it is set up for success or failure. The essence is that your Authority and Accountability need to be balanced for you to be successful in your career, regardless of your station. Everybody from the hospitalist fresh out of residency to the CEO needs to have Authority and Accountability in balance to be successful. And as you use the tool to measure your own potential for success or failure, learn to apply it to those who report to you.

I believe the rising tide lifts all boats and the success of your subordinates, through mentoring and support, will add to your success. There is another, more cynical view of subordinates that can be identified using the Authority/Accountability balance, which I will address.

Authority

In this construct, "Authority" has a much broader meaning than just the ability to tell people what to do. The ability to tell people what to do is important but not sufficient for success in hospital politics.

Financial resources are essential for a successful Authority/Accountability balance – not only the hardware such as computers, telephones, pagers, and so on, but also clerical support, technical support, and analytic support so that you are getting high-quality data on the performance of the members of your hospital medicine group (HMG). These "soft" resources (clerical, technical, and analytical) are often overlooked as needs that HMG leaders must advocate for; I speak with many HMG leaders who remain under-resourced with "soft" assets. However, being appropriately resourced in these areas can be transformational for a group. Hospitalists don't like doing clerical work, and if you don't like a menial job assigned to you, you probably won't do it very well. Having an unlicensed person dedicated to these clerical activities not only will cost less, but will ensure the job is done better.

Reporting structure is critically important, often overlooked, and historically misaligned in HMGs. When hospital medicine was starting in the late 1990s and early 2000s, rapidly growing hospitalist groups were typically led by young, early-career physicians who had chosen hospital medicine as a career. The problem was that they often lacked the seniority and connections at the executive level to advocate for their HMG. All too often the hospitalist group was tucked in under another department or division which, in turn, reported HMG updates and issues to the board of directors and the CEO.

A common reporting structure in the early days was that a senior member of the medical staff, or group, had once worked in the hospital and therefore "understood" the issues and challenges that the hospitalists were facing. It was up to this physician with seniority and connections to advocate for the hospitalists as they saw fit. The problem was that the hospital landscape was, and is, constantly evolving in innumerable ways. These "once removed" reporting structures for HMGs failed to get the required information on the rapidly changing, and evolving, hospitalist landscape to the desks of executives who had the financial and structural control to address the challenges that the hospitalists in the trenches were facing.

Numerous HMGs failed in the early days of hospital medicine because of this type of misaligned reporting structure. This is a lesson that should not be forgotten: Make sure your HMG leader has a seat at the table where executive decisions are made, including but not limited to the board of directors. To be in balance, you have to be "in the room where it happens."

Accountability

The outcomes that you are responsible for need to be explicit, appropriately resourced with Authority, and clearly spelled out in your job description. Your job description is a document you should know, own, and revisit regularly with whomever you report to, in order to ensure success.

Once you have the Authority side of the equation appropriately resourced, setting outcomes that are a stretch, but still realistic and achievable within the scope of your position, is critical to your success. It is good to think about short-, medium-, and long-term goals, especially if you are in a leadership role. For example, one expectation you will have, regardless of your station, is that you keep up on your email and answer your phone. These are short-term goals that will often be included in your job description. However, taking on a new hospital contract and making sure that it has 24/7 hospitalist coverage, that all the hospitalists are meeting the geometric mean length of stay, and that all the physicians are having 15 encounters per day doesn't happen immediately. Long-term goals, such as taking on a new hospital contract, are the big-picture stuff that can make or break the career of an HMG leader. Long-term goals also need to be delineated in the job description, along with specific time stamps and the resources you need to accomplish big-ticket items – which are spelled out in the Authority side (that is, physician recruiter, secretary, background checks, and so on).

One of the classic misuses of Accountability is the "Fall Guy" scenario. The Fall Guy scenario is often used by cynical hospital and medical group executives to expand their influence while limiting their liability. In the Fall Guy scenario, the executive is surrounded with junior partners who are underpowered with Authority, and then the executive makes decisions for which the junior partners are Accountable. This allows the senior executive to make risky decisions on behalf of the hospital or medical group without the liability of being held accountable when the decision-making process fails. When the risky, and often

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"Long-term goals, such as taking on a new hospital contract, are the big-picture stuff that can make or break the career of an HMG leader. Long-term goals also need to be delineated in the job description, along with specific time stamps and the resources you need."

ill-informed, decision fails, the junior partner who lacked the Authority to make the decision – but held the Accountability for it – becomes the Fall Guy for the failed endeavor. This is a critical outcome that the Authority/Accountability balance can help you avoid, if you use it wisely and properly.

If you find yourself in the Fall Guy position, it is time for a change. The Authority, the Accountability, or both need to change so that they are in better balance. Or your employer needs to change. Changing employers is an outcome worth avoiding, if at all possible. I have scrutinized thousands of resumes in my career, and frequent job changes always wave a red flag to prospective employers. However, changing jobs remains a crucial option if you are being set up for failure when Authority and Accountability are out of balance.

If you are unable to negotiate for the balance that will allow you to be successful with your current group, remember that HMG leaders are a prized commodity and in short supply. Leaving a group that has been your career is hard, but it is better to leave than stay in a position where you are set up for failure as the Fall Guy. Further, the most effective time to expand your Authority is when you are negotiating the terms of a new position. Changing positions is the nuclear option. However, it is better than becoming the Fall Guy, and a change can create opportunities that will accelerate your career and influence, if done right.

When I talk about Authority/Accountability balance, I always counter the Fall Guy with an ignominious historical figure: General George B. McClellan. General McClellan was the commander of the Army of the Potomac during the early years of the American Civil War. General McClellan had the industrial might of the Union north at his beck and call, as well as extraordinary resources for recruiting and retaining soldiers for his army. At every encounter with General Robert E. Lee's Army of Northern Virginia, General McClellan outnumbered them, sometimes by more than two to one. Yet General McClellan was outfoxed repeatedly for the same reason: He failed to take decisive action.

Every time that McClellan failed, he blamed insufficient resources and told President Lincoln that he needed more troops and more equipment to be successful. In summary, while the Fall Guy scenario needs to be avoided, once you are adequately resourced, success requires taking decisive and strategic action, or you will suffer as did General McClellan. Failing to act when you are appropriately resourced can be just as damaging to your career and credibility as allowing yourself to become the Fall Guy.

DrAfter123/Getty Images

Job description

Everybody has somebody that they report to, no matter how high up on the executive ladder they have climbed. Even the CEO must report to the board of directors. And that reporting structure usually involves periodic formal reviews. Your formal review is a good time to go over your job description, note what is relevant, remove what is irrelevant, and add new elements that have evolved in importance since your last review.

> *"Despite my cynicism toward executives in the medical field, I personally advocate for supporting the career development of those around you and advise against furthering your career at the expense of others."*

Job descriptions take many forms, but they always include a list of qualifications. If you have the job, you have the qualifications, so that is not likely to change. You may become more qualified for a higher-level position, but that is an entirely different discussion. I like to think of a well-written job description as including short-term and long-term goals. Short-term goals are usually the daily stuff that keeps operations running smoothly but garners little attention. Examples would include staying current on your emails, answering your phone, organizing meetings, and regularly attending various committees. Even some of these short-term goals can and will change over time. I always enjoyed quality oversight in my department, but as the department and my responsibilities grew, I realized I couldn't do everything that I wanted to do. I needed to focus on the things only I could do and delegate those things that could be done by someone else, even though I wanted to continue doing them myself. I created a position for a clinical quality officer, and quality oversight moved off of my job description.

Long-term goals are the aspirational items, such as increasing market share, decreasing readmissions, improving patient satisfaction, and the like. Effective leaders are often focused on these aspirational, long-term goals, but they still must effectively execute their short-term goals. Stephen Covey outlines the dilemma with the "time management matrix" in his seminal work "The 7 Habits of Highly Effective People." An in-depth discussion is beyond the scope of this article, but the time management matrix places tasks into one of four categories based on urgency and importance, and provides strategies for staying up on short-term goals while continually moving long-term goals forward.

If you show up at your review with a list of accomplishments as well as an understanding of how the "time management matrix" affects your responsibilities, your boss will be impressed. It is also worth mentioning that Covey's first habit is "Proactivity." He uses the term Proactivity in a much more nuanced form than we typically think of, however. Simply put, Proactivity is the opposite of Reactivity, and it is another invaluable tool for success with those long-term goals that will help you make a name for yourself.

When you show up for your review, be it annual, biannual, or other, be prepared. Not only should you bring your job description and recommendations for how it should be adapted in the changing environment, but also bring examples of your accomplishments since the last review.

I talk with leaders frequently who are hardworking and diligent and hate bragging about their achievements; I get that. At the same time, if you don't inform your superiors about your successes, there is no guarantee that they will hear about them or understand them in the appropriate context. Bragging about how great you are in the physician's lounge is annoying; telling your boss about your accomplishments since the last review is critical to maintaining

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Hospitalists and unit-based assignments

By Isha Puri, MD, MPH, FHM

What seems like a usual day to a seasoned hospitalist can be a daunting task for a new hospitalist. A routine day as a hospitalist begins with prerounding, organizing, familiarizing, and gathering data on the list of patients, and most importantly prioritizing the tasks for the day. I have experienced both traditional and unit-based rounding models, and the geographic (unit-based) rounding model stands out for me.

The push for geographic rounding comes from the need to achieve excellence in patient care, coordination with nursing staff, higher HCAHPS (Hospital Consumer Assessment of Healthcare Providers and Systems) scores, better provider satisfaction, and efficiency in work flow and in documentation. The goal is typically to use this well-established tool to provide quality care to acutely ill patients admitted to the hospital, creating an environment of improved communication with the staff. It's a "patient-centered care" model – if the patient wants to see a physician, it's quicker to get to the patient and provides more visibility for the physician. These encounters result in improved patient-provider relationships, which in turn influences HCAHPS scores. Proximity encourages empathy, better work flow, and productivity.

The American health care system is intense and complex, and effective hospital medicine groups (HMGs) strive to provide quality care. Performance of an effective HMG is often scored on a "balanced score card." The "balanced score" evaluates performance on domains such as clinical quality and safety, financial stability, HCAHPS, and operational effectiveness (length of stay and readmission rates). In my experience, effective unit-based rounding positively influences all the measures of the balanced score card.

Multidisciplinary roundings (MDRs) provide a platform where "the team" meets every morning to discuss the daily plan of care, everyone gets on the same page, and unit-based assignments facilitate hospitalist participation in MDRs. MDRs typically are a collaborative effort between care team members, such as a case manager, nurse, and hospitalist, physical therapist, and pharmacist. Each team member provides a precise input. Team members feel accountable and are better prepared for the day. It's easier to develop a rapport with your patient when the same organized, comprehensive plan of care gets communicated to the patient.

It is important that each team member is prepared prior to the rounds. The total time for the rounds is often tightly controlled, as a fundamental concern is that MDRs can take up too much time. Use of a checklist or whiteboard during the unit-based rounds can improve efficiency. Midday MDRs are another gem in patient care, where the team proactively addresses early barriers in patient care and discharge plans for the next day.

The 2020 *State of Hospital Medicine* report highlights utilization of unit-based rounding, including breakdowns based on employment model. In groups serving adults patients only, 43% of university/medical school practices utilized unit-based assignments versus 48% for hospital-employed HMGs and only 32% for HMGs employed by multistate management companies. In HMGs that served pediatric patients only, 27% utilized unit-based assignments.

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Undoubtedly geographic rounding has its own challenges. The pros and cons and the feasibility needs to be determined by each HMG. It's often best to conduct the unit-based rounds on a few units and then roll it out to all the floors.

An important prerequisite to establishing a unit-based model for rounding is a detailed data analysis of total number of patients in various units to ensure there is adequate staffing. It

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the momentum of past accomplishments. If you are not willing to toot your own horn, there is a very good chance that your horn will remain silent. I don't think self-promotion comes easily to anyone, and it has to be done with a degree of humility and sensitivity; but it has to be done, so prepare for it.

Importance of teamwork

We talk about teamwork and collaboration as hospitalists, and SHM is always underscoring the importance of teamwork and highlighting examples of successful teamwork in its many conferences and publications. Most hospital executives are focused on their own careers, however, and many have no reservations about damaging your career (your brand) if they think it will promote theirs. You have to look out for yourself and size up every leadership position you get into.

Physicians can expect their careers to last decades. The average hospital CEO has a tenure of less than 3.5 years, however, and when a new CEO is hired, almost half of chief financial, chief operating, and chief information officers are fired within 9 months. You may be focused on the long-term success of your organization as you plan your career, but many hospital administrators are interested only in short-term gains. It is similar to some members of Congress who are interested only in what they need to do now to win the next election and not in the long-term needs of the country. You should understand this disconnect when dealing with hospital executives, and how you and your credibility can become cannon fodder in their quest for short-term self-preservation.

You have to look out for and take care of yourself as you promote your group. With a better understanding of the Authority/Accountability balance, you have new tools to assess your chances of success and to advocate for yourself so that you and your group can be successful.

Despite my cynicism toward executives in the medical field, I personally advocate for supporting the career development of those around you and advise against furthering your career at the expense of others. Many unscrupulous executives will use this approach, surrounding themselves with Fall Guys, but my experience shows that this is not a sustainable strategy for success. It can lead to short-term gains, but eventually the piper must be paid. Moreover, the most successful medical executives and leaders that I have encountered have been those who genuinely cared about their subordinates, looked out for them, and selflessly promoted their careers.

In the age of social media, tearing others down seems to be the fastest way to get more "likes." However, I strongly believe that you can't build up your group, and our profession, just by tearing people down. Lending a helping hand may bring you less attention in the short term, but such action raises your stature, creates loyalty, and leads to sustainable success for the long run.

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must be practical to localize providers to different units, and complexity of various units can differ. At Lahey Hospital and Medical Center in Burlington, Mass., an efficient unit-based model has been achieved with complex units typically assigned two providers. Units including oncology and the progressive care unit can be a challenge, because of higher intensity and patient turnover.

Each unit is tagged to another unit in the same geographical area; these units are designated "sister pods." The intention of these units is to strike a balance and level off patient load when needed. This process helps with standardization of the work between the providers. A big challenge of the unit-based model is to understand that it's not always feasible to maintain consistency in patient assignments. Some patients can get transferred to a different unit because of limited telemetry and specialty units. At Lahey the provider manages their own patient as "patient drift" happens, in an attempt to maintain continuity of care.

The ultimate goal of unit-based assignments is to improve quality, financial, and operational metrics for the organization and take a deeper dive into provider and staff satisfaction. The simplest benefit for a hospitalist is to reduce travel time while rounding.

Education and teaching opportunities during the daily MDRs are still debatable. Another big step in this area may be a "resident-centered MDR" with the dual goals of improving both quality of care and resident education by focusing on evidence-based medicine.

Utilization of Unit-Based Assignments

	Total Groups	Yes	No
Pediatric Only	95	27.4%	72.6%
Employment Model			
Hospital, Health System or Integrated Delivery System	56	25.0%	75.0%
University, Medical School or Faculty Practice	31	25.8%	74.2%

This table was taken from the 2020 *SoHM* Report.

Utilization of Unit-Based Assignments

	Total Groups	Yes	No
Adults Only	368	42.7%	57.3%
Employment Model			
Hospital, Health System or IDS	202	48.5%	51.5%
Private Local/Regional HMG	13	38.5%	61.5%
Multistate Management Company	90	32.2%	67.8%
Private Multispecialty or Primary Care Group	14	35.7%	64.3%
University, Med School or Faculty Practice	42	42.9%	57.1%

Footnote

The Survey question for this table asked whether the group used unit-based assignments (geographic rounding) for some or all of its hospitalists but excluded observation units as these are commonly staffed by hospitalists. Larger groups tended to have unit-based assignments.

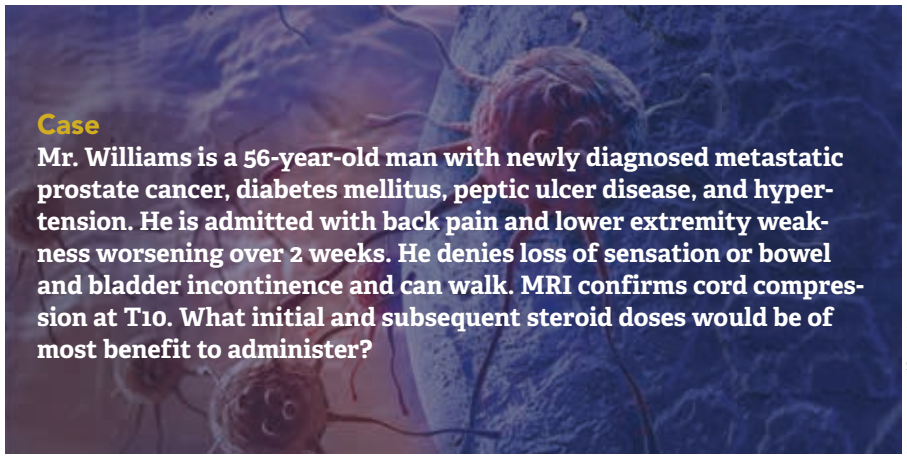
This table was taken from the 2020 *SoHM* Report.

Key Clinical Question

How do you manage common inpatient oncologic emergencies?

Three routinely encountered emergencies in the inpatient setting

By Krishna A. Chokshi, MD; and Cardinale Smith, MD, PhD



Case

Mr. Williams is a 56-year-old man with newly diagnosed metastatic prostate cancer, diabetes mellitus, peptic ulcer disease, and hypertension. He is admitted with back pain and lower extremity weakness worsening over 2 weeks. He denies loss of sensation or bowel and bladder incontinence and can walk. MRI confirms cord compression at T10. What initial and subsequent steroid doses would be of most benefit to administer?

HISPANOLISTIC/GETTY IMAGES

In 2016, there were an estimated 15,338,988 people living with cancer in the United States.[1] As such, it is important that hospitalists be proficient in managing oncologic emergencies that can arise during the natural history of cancer or from its treatment. This article will review three emergencies that are routinely encountered in the inpatient setting: malignant spinal cord compression (MSCC), hypercalcemia of malignancy (HCM), and febrile neutropenia (FN).

Malignant spinal cord compression

Treatment of MSCC usually aims to preserve function rather than reverse established deficits. MSCC from epidural tumor metastasis develops in 5%-14% of all cancer cases,[2] with back pain as the most common symptom. Nearly 60%-85% of patients have weakness at the time of diagnosis,[3] and unfortunately, nearly two-thirds of patients will be nonambulatory at presentation.

While timely steroid administration in addition to definitive treatment may maintain ambulatory capacity at 1 year after therapy,[4] there is no consensus on the optimal loading and maintenance dose and duration of steroids.

Overview of the data

Although there are no formal guidelines on optimal steroid dosing for MSCC, it is common practice for dexamethasone to be initially dosed at 10 mg followed by 4 mg every 4-6 hours.[5] The use of higher doses of dexamethasone may result in improvement in neurologic deficits, but has higher risks for toxicity and is not universally supported in the literature.

A study conducted by Vecht and colleagues demonstrated few differences between initial high-dose and low-dose dexamethasone.[6] Intravenous administration of either 10 mg or 100 mg dexamethasone, both followed by total 16 mg of dexamethasone orally per day, showed no significant difference in mobility or survival between the groups.

In a prospective study by Heimdal and colleagues that evaluated the relationship between dexamethasone dose and toxicity, higher doses of steroids had no meaningful impact on neurological symptoms and resulted in more severe side effects.[7] Patients were either given a 96-mg IV loading dose, gradually tapered over 2 weeks, or enrolled in the low-dose group in which they received 4 mg IV dexamethasone four times per day with a taper over 2 weeks. The high-dose group experienced side effects in 28.6% of patients, with 14.3% experiencing serious side effects.

Meanwhile, 7.9% of the low-dose group exhibited some side effects, with none experiencing serious adverse effects. The high-dose group did not experience a significant increase in mobility (57.1% vs. 57.9%).

Key takeaways

Dexamthasone 10 mg oral or IV followed by 4 mg every 4-6 hours until definitive treatment is started is associated with improved neurologic outcomes and minimal adverse side effects. Higher doses of steroids are unlikely to offer more benefit. In patients with paraplegia or autonomic dysfunction, the ability to restore neurologic function is reduced and the burdens of steroid treatment may outweigh its benefits.[5]

Case continued

Mr. Williams completed treatment for MSCC but was still complaining of extreme lethargy and noticed an increase in thirst and no bowel movement in 5 days. His serum calcium was 14 mg/dL.

Hypercalcemia of malignancy

HCM is the most common paraneoplastic syndrome, observed in nearly 30% of patients with advanced cancer. It is a poor prognostic indicator, and approximately half of all patients with HCM will die within 30 days.[8] Cancer is the most common reason for hypercalcemia in the inpatient setting[9] and is most often associated with multiple myeloma, non–small cell lung cancer, breast cancer, renal cell carcinoma, non-Hodgkins lymphoma, and leukemia.

Hypercalcemia most often presents with cognitive changes and lethargy, anorexia, nausea, constipation, polyuria and polydipsia, and renal failure. Bradycardia and shortened QT interval are seen more with severe hypercalcemia.

Dr. Chokshi

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Management of hypercalcemia of malignancy

Management of HCM depends on corrected calcium or ionized calcium levels, chronicity, degree of symptoms, and presence of renal failure. In general, mild asymptomatic hypercalcemia can be managed with outpatient care. Serum calcium greater than 14 mg/dL should be treated regardless of symptoms (Table 1).

For mild to moderate HCM, management involves saline administration to achieve euvolemia and calcitonin, which has temporizing effects. Early administration of IV

TABLE 1

Management of hypercalcemia of malignancy

Serum calcium	Severity	Management approach
10.5-11.9 mg/dL	Mild	If the patient is asymptomatic and hypercalcemia developed chronically, it may not require urgent treatment; can usually treat with isotonic fluids.
12.0-13.9 mg/dL	Moderate	Isotonic fluids alone are usually insufficient; can use calcitriol with bisphosphonate therapy.
>14 mg/dL	Severe	Should be treated even in patients without symptoms. Management is similar to moderate hypercalcemia. If >18 mg/dL, worsening renal failure, or inability to tolerate IV fluid, may need to consider dialysis.

Source: Dr. Chokshi, Dr. Smith

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TABLE 2

Agents used for the treatment of hypercalcemia of malignancy

Agent	Indication	Mechanism of action	Dosing	Onset of activity	Duration	Adverse effects
Normal saline	All severity of HCM. Goal is to achieve euvolemia.	Volume expansion; increases renal excretion of Ca.	200-300 mL/hr with goal urinary output >100-150 mL/hr	6 hours	Hours	Hypervolemia. Caution in oliguria or heart failure.
Calcitonin	Temporizes hypercalcemia. Reduces serum calcium by roughly 1 mg/dL. To be given concurrent to bisphosphonates.	Inhibits osteoclast activity; increases renal excretion of Ca; inhibits GI absorption of Ca.	4-8 units/kg IM or subcutaneously	2 hours	6-8 hours	Nausea, flushing, hypersensitivity, local reaction symptoms, hypophosphatemia, nephrotoxicity.
Pamidronate	Moderate to severe HCM.	Inhibits osteoclast activity.	60-90 mg IV administered over 2-6 hours	<24 hours	7-14 days	Osteonecrosis of jaw with long-term use.
Zoledronic acid	Superior to pamidronate in moderate to severe hypercalcemia.	Inhibits osteoclast activity.	4-8 mg IV administered over 15 minutes	24-48 hours	2-3 days	Same as pamidronate. Has been used with creatinine >4.5 mg/dL with dose reduction.
Denosumab	HCM refractory to IV bisphosphonates. HCM in advanced renal failure.	Inhibits RANKL binding to RANK, inhibiting osteoclast formation.	120 mg subcutaneously every 4 weeks w/ loading doses on days 8, 15	9 days	1-4 days	Fatigue, nausea, dermatitis, hypocalcemia hypophosphatemia, worsened in renal failure.
Glucocorticoids	Can be useful for lymphomas that produce 1,25-dihydroxyvitamin D.	Reduces hypercalcemia from calcitriol overproduction.	60 mg by mouth prednisone; hydrocortisone 100 mg every 6 hr	2-5 days	Days to weeks	Hyperglycemia, myopathy, GI bleed.

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Source: Dr. Chokshi, Dr. Smith

bisphosphonates for moderate to severe HCM is beneficial because onset of action is 24-48 hours. Furosemide for management of HCM has fallen out of favor unless the patient develops hypervolemia. Denosumab has been Food and Drug Administration approved for HCM refractory to bisphosphonate therapy and can manage HCM in 64% of patients who did not respond adequately to bisphosphonate therapy.[10] Because it can be used in advanced renal failure without dose adjustment, it is first-line therapy in this population, although the risk for hypocalcemia is increased in renal failure. For patients with serum calcium greater than 18 mg/dL, worsening renal failure, or inability to tolerate IV fluids, dialysis with a low-calcium bath should be considered (Table 2).

Zoledronic acid versus pamidronate

A single dose of zoledronic acid normalizes the serum calcium concentration in 88% of patients, compared with 70% of those who received pamidronate, in a pooled analysis of two phase 3 trials.[11] The median duration of normocalcemia was longer for those receiving zoledronic acid (32-43 days vs. 18 days). The efficacy of the 4-mg and 8-mg zoledronic acid doses were similar, but the 4-mg dose was recommended because of renal toxicity and increased mortality associated with the higher dose. Despite these data, many specialists maintain that pamidronate, which is less expensive, is of similar clinical efficacy to zoledronic acid.[12]

Key takeaways

Management of HCM should be determined by the severity of the calcium level. The mainstay of treatment includes hydration with normal saline, calcitonin ,and bisphosphonate therapy; zoledronic acid is preferred over pamidronate. For patients refractory to bisphosphonates or patients with renal insufficiency, denosumab should be used.

Case continued: Febrile neutropenia

Febrile neutropenia is defined as a single oral temperature of 100.9˚ F or a temperature of 100.4˚ F sustained over a 1-hour period in a patient with absolute neutrophil count (ANC) less than 1,000 cells/mL or ANC expected to decrease to less than 500 cells/mL within a 48-hour period.[13] Up to 30% of patients with solid tumors develop febrile neutropenia after chemotherapy, and nearly 80% of patients with hematologic malignancy or after hematopoietic stem cell therapy (HSCT) experience it.

Even though an infectious etiology is identified in only 30%-40% of cases, all patients with febrile neutropenia should initially receive at least empiric gram-negative coverage. The mortality rate is nearly 70% in neutropenic patients who do not receive empiric antibiotics and is reduced to 4%-20% with antibiotics.[14]

Risk stratification for febrile neutropenia and early discharge

Talcott's Rules, the Multinational Association for Supportive Care in Cancer (MASCC) score, and the Clinical Index of Stable Febrile Neutropenia (CISNE) are validated tools to determine low-risk febrile neutropenia patients (Tables 3 and 4). The Infectious Diseases Society of America guidelines validated the use of MASCC in 2002 but found that CISNE had better performance than other tools. Coyne and colleagues conducted a retrospective cohort study to assess these two risk stratification tools in the ED and found that the CISNE was 98.3% specific for identifying adverse outcomes, whereas the MASCC was 54.2% specific.[15]

A study by Talcott and colleagues used Talcott's Rules to identify low-risk febrile neutropenia patients, who were randomized to early discharge with home intravenous antibiotics versus continued inpatient management. There were no significant differences in the primary outcomes, defined as any change in clinical status requiring medical evaluation.[16] Another study suggested that discharge after 24 hours based on clinical stability

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TABLE 3

Multinational Association for Supportive Care in Cancer index

Characteristic	Weight
Burden of febrile neutropenia with no or mild symptoms[1]	5
No hypotension (systolic BP >90 mmHg)	5
No chronic obstructive pulmonary disease[2]	4
Solid tumor or hematological malignancy with no previous fungal infection[3]	4
No dehydration requiring parenteral fluids	3
Burden of febrile neutropenia with moderate symptoms[4]	3
Outpatient status	3
Age <60 years	2

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1. Burden of febrile neutropenia refers to general clinical status as influenced by the febrile neutropenic episode. It is evaluated in accordance with the following scale: no symptoms (5), mild symptoms (5), moderate symptoms (3), severe symptoms (0), moribund (0).
2. Chronic obstructive pulmonary disease means active chronic bronchitis, emphysema, decrease in FEVs, need for oxygen therapy and/or steroids and/or bronchodilators.
3. Previous fungal infection means demonstrated fungal infection or empirically treated suspected fungal infection.
4. Points attributed to the variable "burden of febrile neutropenia" are not cumulative. Thus, the maximum theoretical score is therefore 26. A score of ≥21 is considered low risk and a score of <21 as high risk (positive predictive value of 91%, specificity of 68%, and sensitivity of 71%).

Source: Ann Emerg Med. 2017;69(6):755-64. doi: 10.1016/j.annemergmed.2016.11.007

TABLE 4

Clinical Index of Stable Febrile Neutropenia

Characteristic	Points
Eastern Cooperative Oncology Group performance score ≥2	2
Stress-induced hyperglycemia (initial blood glucose ≥121 mg/dL, or ≥250 mg/dL in diabetic patients or those on steroids)	2
Chronic obstructive pulmonary disease	1
Chronic cardiovascular disease	1
Mucositis grade ≥2	1
Monocytes <200 cells/mcL	1

Scoring	Interpretation
Low risk = 0	1.1%-1.5% risk of complication within 7 days
Intermediate risk = 1-2	4%-6.2% risk of complication within 7 days
High risk = ≥3	34%-95% risk of complication within 7 days

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Source: Ann Emerg Med. 2017;69(6):755-64. doi: 10.1016/j.annemergmed.2016.11.007

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with outpatient oral antibiotics was noninferior to standard inpatient and intravenous antibiotic therapy.[17] A Cochrane review in 2013 of 22 randomized controlled trials determined that oral antibiotics were an acceptable treatment for low-risk patients.[18]

Key takeaways

Though the MASCC is highly sensitive in identifying low-risk febrile neutropenia patients, it should be used with clinical caution because up to 11% of patients characterized as low risk developed severe complications.[19] If a low-risk patient with solid tumor malignancy has adequate home support, lives within an hour of the hospital, and has access to follow-up within 72 hours, oral antibiotics and early discharge can be considered.

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Quiz

Mrs. Smith is a 64-year-old woman with endometrial cancer with temperature of 100.4˚ F at home. She takes no antibiotics, has no other medical history, and was sent in from clinic and admitted for further management. She feels well, and preliminary infectious workup is negative. She has been afebrile for more than 24 hours, and her ANC is 600 cells/mL.

Her son's soccer game is tomorrow, and she would like to be present. Her family is involved in her care. Under what conditions can she be discharged?

A. She should not be discharged until full course of empiric intravenous antibiotics is completed.
B. Consider discharge in another 24 hours if she remains afebrile.
C. Discharge if low risk by MASCC or CISNE, with oral doses of levofloxacin or moxifloxacin or oral ciprofloxacin and amoxicillin/clavulanic acid.

Answer: C. The patient has a solid tumor malignancy, is low risk by both MASCC and CISNE, and can most likely be discharged if she is clinically stable or improved. A 7-day course of antibiotics is recommended with close follow-up.

Unexpected results in COVID-19 cytokine data

By Damian McNamara

The immune system overactivation known as a "cytokine storm" does not play a major role in more severe COVID-19 outcomes, according to unexpected findings in new research. The findings stand in direct contrast to many previous reports.

"We were indeed surprised by the results of our study," senior study author Peter Pickkers, MD, PhD, said in an interview.

In a unique approach, Dr. Pickkers and colleagues compared cytokine levels in critically ill people with COVID-19 with those in patients with bacterial sepsis, trauma, and after cardiac arrest.

"For the first time, we measured the cytokines in different diseases using the same methods. Our results convincingly show that the circulating cytokine concentrations are not higher, but lower, compared to other diseases," said Dr. Pickkers, who is affiliated with the department of intensive care medicine at Radboud University Medical Center in Nijmegen, the Netherlands.

The team's research was published online on Sept. 3 in a letter in JAMA.

Cytokines lower than expected

Normally, cytokines trigger inflammation and promote healing after trauma, infection, or other conditions.

Although a cytokine storm remains ill defined, the authors noted, many researchers have implicated a hyperinflammatory response involving these small proteins in the pathophysiology of COVID-19.

The question remains, however, whether all cytokine storms strike people with different conditions the same way.

Dr. Pickkers, lead author Matthijs Kox, PhD, and colleagues studied 46 people with COVID-19 and acute respiratory distress syndrome (ARDS) who were admitted to the ICU at Radboud University Medical Center. All participants underwent mechan-

Continued on following page

2020 has been quite a year

By Danielle Scheurer, MD, MSCR, SFHM

I remember New Year's Day 2020, full of hope and wonderment of what the year would bring. I was coming into the Society of Hospital Medicine as the incoming President, taking the 2020 reins in the organization's 20th year. It would be a year of transitioning to a new CEO, reinvigorating our membership engagement efforts, and renewing a strategic plan for forward progress into the next decade. It would be a year chock full of travel, speaking engagements, and meetings with thousands of hospitalists around the globe.

What I didn't know is that we would soon face the grim reality that the long-voiced concern of infectious disease experts and epidemiologists would come true. That our colleagues and friends and families would be infected, hospitalized, and die from this new disease, for which there were no good, effective treatments. That our ability to come together as a nation to implement basic infection control and epidemiologic practices would be fractured, uncoordinated, and ineffective. That within 6 months of the first case on U.S. soil, we would witness 5,270,000 people being infected from the disease, and about 200,000 dying from it. And that the stunning toll of the disease would ripple into every nook and cranny of our society, from the economy to the fabric of our families and to the mental and physical health of all of our citizens.

However, what I couldn't have known on this past New Year's Day is how incredibly resilient and innovative our hospital medicine society and community would be not only to endure this new way of working and living, but also to find ways to improve upon how we care for all patients, despite COVID-19. What I couldn't have known is how hospitalists would pivot to new arenas of care settings, including the EDs, ICUs, "COVID units," and telehealth – flawlessly and seamlessly filling care gaps that would otherwise be catastrophically unfilled.

What I couldn't have known is how we would be willing to come back into work, day after day, to care for our patients, despite the risks to ourselves and our families. What I couldn't have known is how hospitalists would come together as a community to network and share knowledge in unprecedented ways, both humbly and proactively – knowing that we would not have all the answers but that we probably had better answers than most. What I couldn't have known is that the SHM staff would pivot our entire SHM team away from previous "staple" offerings (e.g., live meetings) to virtual learning and network opportunities, which would be attended at rates higher than ever seen before, including live webinars, HMX exchanges, and e-learnings. What I couldn't have known is that we would figure out, in a matter of weeks, what treatments were and were not effective for our patients and get those treatments to them despite the difficulties. And what I couldn't have known is how much prouder I would be, more than ever before, to tell people: "I am a hospitalist."

I took my son to the dentist recently, and when we were just about to leave, the dentist asked: "What do you do for a living?" and I stated: "I am a hospitalist." He slowly breathed in and replied: "Oh … wow … you have really seen things …" Yes, we have.

Dr. Scheurer is chief quality officer and professor of medicine at the Medical University of South Carolina, Charleston. She is president of SHM.

So, is 2020 shaping up as expected? Absolutely not! But I am more inspired, humbled, and motivated than ever to proudly serve SHM with more energy and enthusiasm than I would have dreamed on New Year's Day. And even if we can't see each other in person (as we so naively planned), through virtual meetings (national, regional, and chapter), webinars, social media, and other listening modes, we will still be able to connect as a community and share ideas and issues as we muddle through the remainder of 2020 and beyond. We need each other more than ever before, and I am so proud to be a part of this SHM family.

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ical ventilation and were treated between March 11 and April 27, 2020.

The investigators measured plasma levels of cytokines, including tumor necrosis factor (TNF), interleukin-6, and IL-8. They compared results in this group with those in 51 patients who experienced septic shock and ARDS, 15 patients with septic shock without ARDS, 30 people with out-of-hospital cardiac arrest, and 62 people who experienced multiple traumas. They used historical data for the non–COVID-19 cohorts.

Conditional findings assessed

Compared with patients with septic shock and ARDS, the COVID-19 cohort had lower levels of TNF, IL-6, and IL-8. The differences were statistically significant for TNF ($P < .01$), as well as for IL-6 and IL-8 concentrations (for both, $P < .001$).

In addition, the COVID-19 group had significantly lower IL-6 and IL-8 concentrations compared with the patients who had septic shock without ARDS.

The researchers likewise found lower concentrations of IL-8 in patients with COVID-19, compared with the out-of-hospital cardiac arrest patients. IL-8 levels did not differ between the COVID-19 and trauma groups.

> *"The findings of this preliminary analysis suggest COVID-19 may not be characterized by cytokine storm."*

Furthermore, the researchers found no differences in IL-6 concentrations between patients with COVID-19 and those who experienced out-of-hospital cardiac arrest or trauma.

However, levels of TNF in people with COVID-19 were higher than in trauma patients.

The small sample sizes and single-center study design are limitations.

"The findings of this preliminary analysis suggest COVID-19 may not be characterized by cytokine storm," the researchers noted. However, they added, "whether anticytokine therapies will benefit patients with COVID-19 remains to be determined."

Going forward, Dr. Pickkers and colleagues are investigating the effectiveness of different treatments to lower cytokine levels. They are treating people with COVID-19, for example, with the IL-1 cytokine inhibitor anakinra and steroids.

They also plan to assess the long-term effects of COVID-19 on the immune system. "Following an infection, it is known that the immune system may be suppressed for a longer period of time, and we are determining to what extent this is also present in COVID-19 patients," Dr. Pickkers said.

Enough to cause a storm?

The study "is quite interesting, and data in this paper are consistent with our data," Tadamitsu Kishimoto, MD, PhD, of the department of immune regulation at the Immunology Frontier Research Center at Osaka (Japan) University, said in an interview.

His study, published online Aug. 21 in PNAS, also revealed lower serum IL-6 levels among people with COVID-19, compared with patients with bacterial ARDS or sepsis.

Dr. Kishimoto drew a distinction, however: COVID-19 patients can develop severe respiratory failure, suggesting a distinct immune reaction, compared with patients with bacterial sepsis. SARS-CoV-2 directly infects and activates endothelial cells rather than macrophages, as occurs in sepsis.

For this reason, Dr. Kishimoto said, "SARS-CoV-2 infection causes critical illness and severe dysfunction in respiratory organs and induces a cytokine storm," even in the setting of lower but still elevated serum IL-6 levels.

Dr. Pickkers and Dr. Kishimoto reported no relevant financial relationships.

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Improving communication

Continued from page 1

But if loved ones are going to help patients, they need help from clinicians. Beyond being potential allies, they are also hurting, experiencing worry or confusion in a world of medical jargon.

The coronavirus changes the relationship of patients and their loved ones, as patients are often isolated or limited in the number of visitors they are allowed to see. A smartphone replaces the smiling faces of friends and relatives at their bedside, and a text is a poor substitute for a hug.

The Hospitalist asked some experienced hospitalists for insight on how best to communicate with patients' loved ones to improve outcomes for all, medically and emotionally.

Team approach

"Patients feel isolated, terrified, and vulnerable but still need an advocate in the hospital, so daily communication with a patient's loved one is important to give a sense that the patient is looked after," said Kari Esbensen, MD, PhD, a hospitalist and palliative care expert at Emory University Hospital Midtown, Atlanta.

Glenn Rosenbluth, MD, a pediatric hospitalist and director, quality and safety programs, at the University of California, San Francisco, Benioff Children's Hospital, agreed. He said that the most important thing is to communicate, period.

"We fall into this pattern of 'out of sight, out of mind,'" he said. "We need to take the extra step to find out who a patient's loved ones are. If it is a clinical visit, ask the patient, or maybe get the information from a caseworker, or just pay attention to who is dropping in to see the patient. Having a second person available to jot down notes, or having a handy list of questions – it all helps the patient. We forget that sometimes it can seem like a whirlwind for the patient when they are hurting. We have to remember that a loved one is important to a patient's care team and we need to include them, empower them, and show that we want to hear their voices."

Quick takeaways

- **Get beyond personal protective equipment.** A conversation with a patient's loved one might be easier to achieve via phone, without all the protective gear in the way.
- **Encourage adherence.** Speaking with patients and loved ones together may be more effective. They may reach agreement quicker on how best to adhere to medical advice.
- **Accept clues from loved ones.** They might give you a better sense of a patient's worries, or help you to connect better with those in your care.
- **Be present.** You have a long to-do list but do not let empathy fall off it, even if you feel overwhelmed.
- **Listen.** By finding out what a patient's loved ones know, you can figure out what they don't know – and need to.

Dr. Esbensen said it is critical to start off on the right foot when communicating with a patient's loved one, especially during the current pandemic.

"With COVID-19, the most important thing is to speak honestly, to say hope for the best but prepare for the worst-case scenario," Dr. Esbensen said. "We've seen that conditions can shift dramatically in short periods of time. The loved one needs to have a sense of the positive and negative possibilities. Families tend to lack understanding of the changes in the patient that are caused by COVID-19. The patient can come out of the hospital debilitated, very different than when they entered the hospital, and we need to warn people close to them about this. Unrealistic expectations need to be guarded against if a patient's loved ones are going to help."

Perhaps the best form of communication with a patient's loved ones is an often-forgotten skill: listening.

"Get an idea from the patient's loved ones of what the issues are, as well as their idea of what they think of the disease and how it spreads," Dr. Esbensen said. "Sometimes they are right on target but sometimes there are misinterpretations and we need to help them understand it better. It's not a 'one-size-fits-all' speech that we should give, but try to say, 'tell me what you think is going on, what you think you've heard, and what you're worried about,' and learn what is most important to the patient. Start on those terms and adapt; this way you can correct and address what makes them most fearful, which can be different for each loved one. For some, the concern could be that they have children or other vulnerable people in the house. Finding out these other issues is important."

Venkatrao Medarametla, MD, SFHM, medical director for hospital medicine at Baystate Medical Center, Springfield, Mass., emphasized that, in a time when hospitalists are being pulled in every direction, it is easy to lose your attention.

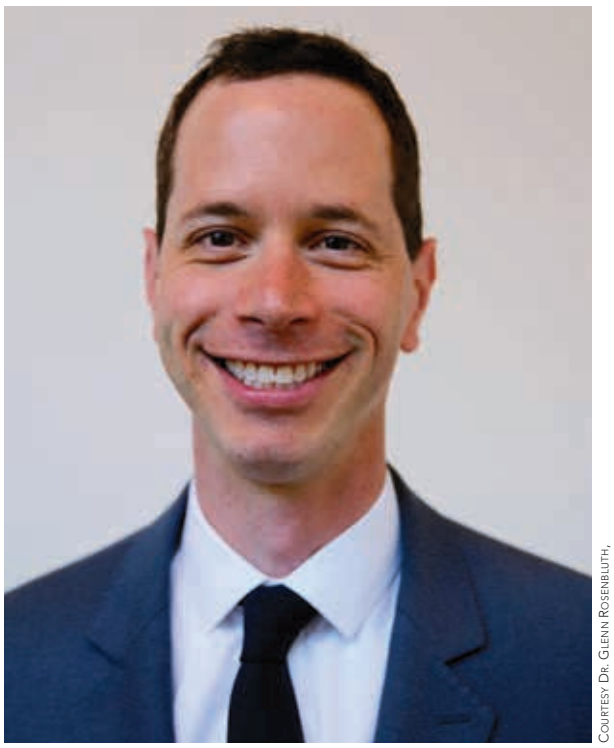
"It's very important that family members know you're present with them," he said. "This can be an emotional time and they need empathy. It's very easy for our list of tasks to get in the way of communicating, including with our body language."

Dr. Medarametla said one of the reasons to communicate with patients' loved ones is to calm them – a patient's relatives or their friends may not be under your medical care, but they are still human beings.

"A lot of people just want information and want to be helpful, but we also need to realize that, while we are caring for many patients, this one person is the patient they are focused on," said Laura Nell Hodo, MD, a pediatric hospitalist at Kravis Children's Hospital at Mount Sinai in New York. "Don't rush, and if you know that a patient's loved one needs more time, make sure it can be found – if not then, at least later on the phone. Fifteen to 20 minutes may be what's needed, and you can't shortchange them."

Dr. Hodo said that a patient's loved ones often do not realize it is possible to receive phone calls from hospitalists. "We need to remind them that they can get in touch with us. We have to remember how helpless they can feel and how they want to understand what is happening in the hospital."

For medical adherence issues, sometimes it is best to communicate with the patient and loved one at the same time, Dr. Hodo advised. "Whether it's for medication or postdischarge exercises, if they both receive the information together it can reinforce adherence. But you also need to remember that the patient may only want a loved one told about certain things, or possibly nothing at all. We need to make sure we understand the patient's wishes, regardless of whether we think a person close to them can be an ally or not."



Courtesy Dr. Glenn Rosenbluth, Dr. Rosenbluth

"We have to remember that a loved one is important to a patient's care team and we need to include them, empower them, and show that we want to hear their voices."

Dr. Esbensen also noted that a loved one can give hospitalists important clues to the emotional components of a patient's care.

"I remember a patient whose wife told me how he worked in a garage, how he was strong and did not want people to think he was a weak guy just because of what was happening to him," Dr. Esbensen said. "I didn't know that he felt he might be perceived in this way. I mentioned to him how I learned he was a good mechanic and he perked up and felt seen in a different light. These things make a difference."

But when is the best time to speak with a

patient's loved ones? Since much communication is done via phone during the pandemic, there are different philosophies.

"We had a debate among colleagues to see how each of us did it," Dr. Rosenbluth said. "Some try to call after each patient encounter, while they are outside the room and it's fresh in their mind, but others find it better to make the call after their rounds, to give the person their full attention. Most of the time I try to do it that way."

Dr. Rosenbluth noted that, in the current environment, a phone call may be better than a face-to-face conversation with patients' loved ones.

"We're covered in so much gear to protect us from the coronavirus that it can feel like a great distance exists between us and the person with whom we're speaking," he said. "It's strange, but the phone can make the conversation seem more relaxed and may get people to open up more."

Courtesy Dr. Laura Nell Hodo

Dr. Hodo

"My experience from working in adult coronavirus units is that the thinking about the loved ones' role in patient care – and communication with them – might just change."

Even when they leave

All the hospitalists affirmed that loved ones can make a big difference for the patient through all aspects of care. Long after a patient returns home, the support of loved ones can have a profound impact in speeding healing and improving long-term outcomes.

Dr. Esbensen said COVID-19 and other serious illnesses can leave a patient needing support, and maybe a "push" when feeling low keeps them from adhering to medical advice.

"It's not just in the hospital but after discharge," she said. "A person offering support can really help patients throughout their journey, and much success in recovering from illness occurs after the transition home. Having the support of that one person a patient trusts can be critical."

Dr. Hodo believes that the coronavirus pandemic could forever change the way hospitalists communicate with patients and their loved ones.

"I work in pediatrics and we know serious medical decisions can't be made without guardians or parents," she said. "But in adult medicine doctors may not automatically ask the patient about calling someone for input on decision-making. With COVID, you cannot assume a patient is on their own, because there are protocols keeping people from physically being present in the patient's room. My experience from working in adult coronavirus units is that the thinking about the loved ones' role in patient care – and communication with them – might just change. … At least, I hope so."

A 'foolproof' way to diagnose narrow complex tachycardias on EKGs

By Bruce Jancin
MDedge News

A hospitalist looking at an EKG showing a narrow complex tachycardia needs to be able to come up with an accurate diagnosis of the rhythm pronto. And hospitalist Meghan Mary Walsh, MD, MPH, has developed a simple and efficient method for doing so within a minute or two that she's used with great success on the wards and in teaching medical students and residents for nearly a decade.

"You're busy on the wards. You may have a patient who's unstable. You need to make diagnostic decisions very rapidly. And this is a foolproof way to make the correct diagnosis every time," she promised at HM20 Virtual, hosted by the Society of Hospital Medicine.

Her method involves asking three questions about the 12-lead EKG:

1) What's the rate?

A narrow complex tachycardia by definition needs to be both narrow and fast, with a QRS complex of less than 0.12 seconds and a heart rate above 100 bpm. Knowing how far above 100 bpm the rate is will help with the differential diagnosis.

2) Is the rhythm regular or irregular?

"If I put the EKG 10 feet away from you, you should still be able to look at it and say the QRS is either systematically marching out – boom, boom, boom – or there is an irregular sea of QRS complexes where the RR intervals are variable and inconsistent," said Dr. Walsh, a hospitalist at the University of Minnesota, Minneapolis, and chief academic officer at Hennepin Healthcare, where she oversees all medical students and residents training in the health system.

This distinction between a regular and irregular rhythm immediately narrows the differential by dividing the diagnostic possibilities into two columns (see chart). She urged her audience to commit the list to memory or keep it handy on their cell phone or in a notebook.

"If it's irregular I'm going down the right column; if it's regular I'm going down the left. And then I'm systematically running the drill," she explained.

3) Are upright p waves present before each QRS complex in leads II and V1?

This information rules out some of the eight items in the differential diagnosis and rules in others.

Narrow complex tachycardias with an irregular rhythm

There are only three:

Atrial fibrillation: The heart rate is typically 110-160 bpm, although it can occasionally go higher. The rhythm is irregularly irregular: No two RR intervals on the EKG are exactly the same. And there are no p waves.

"If it's faster than 100 bpm, irregularly irregular, and no p waves, the conclusion is very simple: It's AFib," Dr. Walsh said.

Multifocal atrial tachycardia (MAT): The heart rate is generally 100-150 bpm but can sometimes climb to about 180 bpm. The PP, PR, and RR intervals are varied, inconsistent, and don't repeat. Most importantly, there are three or more different p-wave morphologies in the same lead. One p wave might look like a tall mountain peak, another could be short and flat, and perhaps the next is big and broad.

MAT often occurs in patients with a structurally abnormal atrium – for example, in the setting of pulmonary hypertension leading to right atrial enlargement, with resultant depolarization occurring all over the atrium.

"Don't confuse MAT with AFib: One has p waves, one does not. Otherwise they can look very similar," she said.

Atrial flutter with variable conduction: A hallmark of this reentrant tachycardia is the atrial flutter waves occurring at about 300 bpm between each QRS complex.

"On board renewal exams, the question is often asked, 'Which leads are the best identifiers of atrial flutter?' And the answer is the inferior leads II, III, and aVF," she said.

Another classic feature of atrial flutter with variable conduction is cluster beating attributable to a varied ventricular response. This results in a repeated pattern of irregular RR intervals: There might be a 2:1 block in AV conduction for several beats, then maybe a 4:1 block for several more, with resultant lengthening of the RR interval, then 3:1, with shortening of RR. This regularly irregular sequence is repeated throughout the EKG.

"Look for a pattern amidst the chaos," the hospitalist advised.

The heart rate might be roughly 150 bpm with a 2:1 block, or 100 bpm with a 3:1 block. The p waves in atrial flutter with variable conduction can be either negatively or positively deflected.

Narrow complex tachycardias with a regular rhythm

Sinus tachycardia: The heart rate is typically less than 160 bpm, the QRS complexes show a regular pattern, and upright p waves are clearly visible in leads II and V1.

The distinguishing feature of this arrhythmia is the ramping up and ramping down of the heart rate. The tachycardia is typically less than 160 bpm. But the rate doesn't suddenly jump from, say, 70 to 140 bpm in a flash while the patient is lying in the hospital bed. A trip to the telemetry room for a look at the telemetry strip will tell the tale: The heart rate will have progressively ramped up from 70, to 80, then 90, then 100, 110, 120, 130, to perhaps 140 bpm. And then it will similarly ramp back down in stages, with the up/down pattern being repeated.

Sinus tachycardia is generally a reflection of underlying significant systemic illness, such as sepsis, hypotension, or anemia.

Atrial tachycardia: The heart rate is generally 100-140 bpm, and p waves are present. But unlike in sinus tachycardia, the patient with atrial tachycardia lying in bed with a heart rate of 140 bpm is not in a state of profound neurohormonal activation and is not all that sick.

Another diagnostic clue is provided by a look at the telemonitoring strip. Unlike in sinus tachycardia, where the heart rate ramps up and then back down repeatedly, in atrial tachycardia the heart rate very quickly ramps up in stages to, say, 140 bpm, and then hangs there.

Atrial flutter: This is the only narrow complex tachycardia that appears in both the regular and irregular rhythm columns. It belongs in the irregular rhythm column when there is variable conduction and cluster beating, with a regularly irregular pattern of RR intervals. In contrast, when atrial flutter is in the regular rhythm column, it's because the atrioventricular node is steadily conducting the atrial depolarizations at a rate of about 300 bpm. So there's no cluster beating. As in atrial flutter with variable conduction, the flutter waves are visible most often in leads II, III, and aVF, where they can be either positively or negatively deflected.

AV reentrant tachycardias: These

Continued on following page

Narrow complex tachycardias: Here's the breakdown

The differential diagnosis	
Regular rhythm	**Irregular rhythm**
1) Sinus tachycardia	1) Atrial fibrillation
2) Atrial tachycardia	2) Multifocal atrial tachycardia
3) Atrial flutter	3) Atrial flutter with variable conduction
4) AV reentrant tachycardias	
5) Accelerated junctional rhythm	

Source: Dr. Walsh

MDedge News

Risk stratification key in acute pulmonary embolism

By Bruce Jancin
MDedge News

All intermediate-risk pulmonary embolism is not the same, Victor F. Tapson, MD, declared at HM20 Virtual, hosted by the Society of Hospital Medicine.

The best current guidelines on the management of acute pulmonary embolism (PE) recommend a risk stratification strategy that involves further subdivision of intermediate-risk PE into intermediate to low or intermediate to high risk. This additional classification is worthwhile because it has important treatment implications.

Patients with intermediate- to low-risk PE, along with those who have truly low-risk PE, require anticoagulation only. In contrast, patients with intermediate- to high-risk PE are at increased risk of decompensation. They have a much higher in-hospital mortality than those with intermediate- to low-risk PE. So hospitalists may want to consult their hospitals' PE response team (PERT), if there is one, or whoever on staff is involved in helping make decisions about the appropriateness of more aggressive interventions, such as catheter-directed thrombolysis or catheter-directed clot extraction, said Dr. Tapson, director of the venous thromboembolism and pulmonary vascular disease research program at Cedars-Sinai Medical Center in Los Angeles.

"We don't have evidence of any real proven mortality difference yet in the intermediate- to high-risk PE group by being more aggressive. I think if the right patients were studied we could see a mortality difference. But one thing I've noted is that by being more aggressive – in a cautious manner, in selected patients – we clearly shorten the hospital stay by doing catheter-directed therapy in some of these folks. It saves money," he observed.

Once the diagnosis of PE is confirmed, the first priority is to get anticoagulation started in all patients with an acceptable bleeding risk, since there is convincing evidence that anticoagulation reduces mortality in PE. The 2019 European Society of Cardiology guidelines recommend a direct-acting oral anticoagulant over warfarin on the basis of persuasive evidence of lower risk of major bleeding coupled with equal or better effectiveness in preventing recurrent PE.

Dr. Tapson said it's worthwhile for hospitalists to take a close look at these European guidelines (Eur Respir J. 2019 Oct 9. doi: 10.1183/13993003.01647-2019).

"I think our Europeans friends did a really nice job with those guidelines. They're great guidelines, better than many of the others out there. I think they're very, very usable," he said. "I took part in the ACCP [American College of Chest Physicians] guidelines for years. I think they're very rigorous in terms of the evidence base, but because they're so rigorous there's just tons of 2C recommendations, which are basically suggestions. The ESC guidelines are more robust."

Risk stratification

Once anticoagulation is on board, the next task is risk stratification to determine the need for more aggressive therapy. A high-risk PE is best defined hemodynamically as one causing a systolic blood pressure below 90 mm Hg for at least 15 minutes. The term "high risk" is increasingly replacing "massive" PE, because the size of the clot doesn't necessarily correlate with its hemodynamic impact.

An intermediate-risk PE is marked by a simplified Pulmonary Embolism Severity Index (sPESI) score of 1 or more, right ventricular dysfunction on echocardiography or CT angiography, or an elevated cardiac troponin level.

The sPESI is a validated, user-friendly tool that grants 1 point each for age over 80, background cardiopulmonary disease, a systolic blood pressure below 100 mm Hg, cancer, a heart rate of 110 bpm or more, and an oxygen saturation level below 90%.

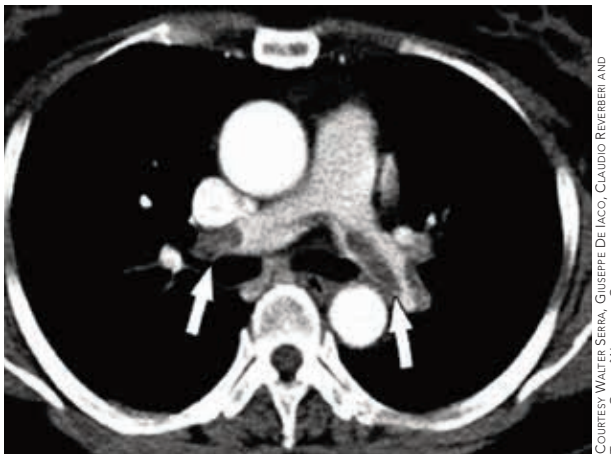
"All you really need to know about a patient's sPESI score is: Is it more than zero?" he explained.

Indeed, patients with an sPESI score of 0 have a 30-day mortality of 1%. With a score of 1 or more, however, that risk jumps to 10.9%.

No scoring system is 100% accurate, though, and Dr. Tapson emphasized that clinician gestalt plays an important role in PE risk stratification. In terms of clinical indicators of risk, he pays special attention to heart rate.

"I think if I had to pick the one thing that drives my decision the most about whether someone needs more aggressive therapy than anticoagulation, it's probably heart rate," he said. "If the heart rate is 70, the patient is probably very stable. Of course, that might not hold up in a patient with conduction problems or who is on a beta-blocker, but in general if I see someone who looks good, has a relatively small pulmonary embolism, and a low heart rate, it makes me feel much better. If the heart rate is 130 or 120, I'm much more concerned."

Both the European guidelines and the PERT Consortium guidelines on the diagnosis, treatment, and follow-up of acute PE



Courtesy Walter Serra, Giuseppe De Iaco, Claudio Reverberi and Tiziano Gherli/Wikimedia Commons

Patients with intermediate- to high-risk PE are at increased risk of decompensation.

(Clin Appl Thromb Hemost. 2019 Jun 17. doi: 10.1177/1076029619853037), which Dr. Tapson coauthored, recommend substratifying intermediate-risk PE into intermediate to low or intermediate to high risk. It's a straightforward matter: If a patient has either right ventricular dysfunction on imaging or an elevated cardiac troponin, that's an intermediate- to low-risk PE warranting anticoagulation only. On the other hand, if both right ventricular dysfunction and an elevated troponin are present, the patient has an intermediate- to high-risk PE. Since this distinction translates to a difference in outcome, a consultation with PERT or an experienced PE interventionalist is in order for the intermediate- to high-risk PE, he said.

Dr. Tapson reported receiving research funding from Bayer, Bristol-Myers Squibb, Janssen, BiO2, EKOS/BTG, and Daiichi. He is also a consultant to Janssen and BiO2, and on speakers' bureaus for EKOS/BTG and Janssen.

Continued from previous page

reentrant tachycardias can take two forms. In atrioventricular nodal reentrant tachycardia (AVnRT), the aberrant pathway is found entirely within the AV node, whereas in atrioventricular reentrant tachycardia (AVRT) the aberrant pathway is found outside the AV node. AVnRT is more common than AVRT. As in atrial flutter, there is no ramp up in heart rate. Patients will be lying in their hospital bed with a heart rate of, say, 80 bpm, and then suddenly it jumps to 180, 200, or even as high as 240 bpm "almost in a split second," Dr. Walsh said.

No other narrow complex tachycardia reaches so high a heart rate. In both of these reentrant tachycardias the p waves are often buried in the QRS complex and can be tough to see. It's very difficult to differentiate AVnRT from AVRT except by an electrophysiologic study.

Accelerated junctional tachycardia: This is most commonly the slowest of the narrow complex tachycardias, with a heart rate of less than 120 bpm.

"In the case of accelerated junctional tachycardia, think slow, think 'regular,' think of a rate often just over 100, usually with p waves after the QRS that are inverted because there's retrograde conduction," she advised.

Dr. Walsh reported having no financial conflicts of interest regarding her presentation.

Batten down the hatches for thyroid storm

By Bruce Jancin
MDedge News

Thyroid storm is a life-threatening endocrine emergency for which, remarkably, there are no definitive diagnostic tests, and the management of which is supported by a startlingly weak evidence base.

"What's tricky is there really are no specific biochemical level cutoffs for thyroid storm, and also no unique laboratory abnormalities. So in the end, it's a clinical diagnosis and a clinical judgment," Stephanie B. Mayer, MD, MHSc, observed at HM20 Virtual, hosted by the Society of Hospital Medicine.

Moreover, there are no prospective clinical trials addressing the treatment of thyroid storm, and the 2016 American Thyroid Association clinical practice guidelines on the topic are based upon low-quality evidence from case reports and studies dating back to the 1970s and 1980s. UpToDate reached the same conclusion in 2020, noted Dr. Mayer, an endocrinologist at Virginia Commonwealth University, Richmond.

Thinking that perhaps the guideline writing panel had missed something, she asked a university medical research librarian to custom-build a comprehensive search for studies on thyroid storm management. The search proved unrewarding, she said.

"The evidence is, unfortunately, a little disappointing," Dr. Mayer explained.

Thyroid storm is a rare condition, but one that hospitalists must be ready for. Dr. Mayer highlighted current best practices in diagnosis and management.

A high-mortality emergency

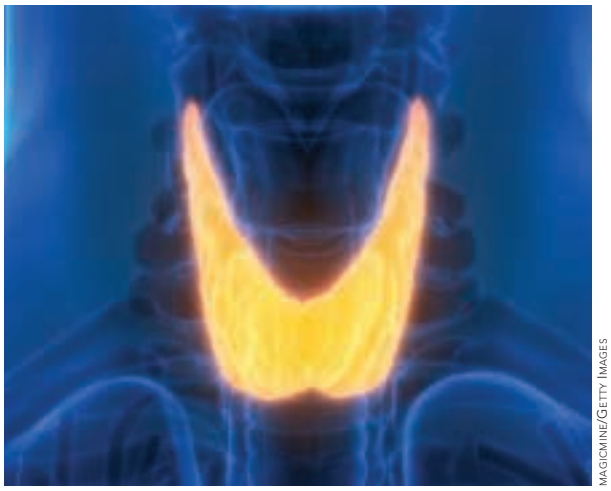
Thyroid storm is an extreme manifestation of thyrotoxicosis, which is marked by multiorgan dysfunction and rapid decompensation. In a large, first-of-its-kind, national retrospective U.S. study, the incidence of thyroid storm was 0.57-0.76 cases per 100,000 persons per year. Thyroid storm accounted for 16% of the more than 121,000 hospital discharges featuring a primary diagnosis of thyrotoxicosis. The in-hospital mortality rate for patients with thyroid storm was 1.2%-3.6% during the 10-year study period, a rate 12-fold higher than that among patients with thyrotoxicosis without thyroid storm (Thyroid. 2019 Jan;29[1]:36-43).

Dr. Mayer highlighted a multicenter French study that underscored the current hefty morbidity and mortality associated with thyroid storm. Among 92 patients admitted to the ICU for thyroid storm, the in-ICU mortality rate was 17%, and the mortality rate 6 months after admission was 22%. Independent risk factors for in-ICU mortality were multiorgan failure and the occurrence of cardiogenic shock within the first 48 hours in the ICU (Crit Care Med. 2020 Jan;48[1]:83-90).

Diagnosis of thyroid storm

The most user-friendly system for assistance in diagnosing thyroid storm is the one put forth by the Japan Thyroid Association and the Japan Endocrine Society, in Dr. Mayer's view. As a prerequisite to the diagnosis a patient must have thyrotoxicosis as evidenced by elevated free thyroxine (free T4) and free or total triiodothyronine (T3), which in the vast majority of cases, is accompanied by low thyroid-stimulating hormone (TSH).

The Japanese diagnostic system for thyroid storm relies on five categories of organ system–based clinical features. This approach places greater weight on disturbances of consciousness – restlessness, delerium, agitation, psychosis, lethargy, coma – than the other four components, which consist of fever of at least 100.4° F, tachycardia of 130 or more beats per minute, heart failure signs and symptoms, and gastrointestinal/hepatic involvement as evidenced by nausea, vomiting, hyperdefecation, and/or a total bilirubin level of 3.0 mg/dL or more.



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The Japanese approach offers two paths to a definite diagnosis of thyroid storm. One requires at least one CNS manifestation plus symptoms drawn from any one of the other four categories. The other route, for patients without evident CNS symptoms, requires the presence of symptoms from at least three of the other four categories, Dr. Mayer said.

A patient is categorized as having suspected rather than definite thyroid storm if the CNS criterion isn't met but any two of the others are. A patient also qualifies for suspected thyroid storm when CNS manifestations plus symptoms from at least one other category are present, but thyroid hormone levels aren't available (Endocr J. 2016 Dec 30;63[12]:1025-64).

Management of thyroid storm

There is usually a precipitating event that drives the transition from smoldering thyrotoxicosis to thyroid storm.

"The big thing is to look for and treat the underlying precipitating event," the endocrinologist stressed.

It's often a systemic insult: severe infection, trauma, surgery, an acute MI, diabetic ketoacidosis, pulmonary embolism, or perhaps having just gone through labor. Iodine exposure in the form of IV contrast or taking amiodarone, which contains 37% iodine by weight, can also fan thyrotoxicosis into thyroid storm. Abrupt discontinuation of antithyroid medication is another common cause.

Fluid and electrolyte replacement, oxygen if appropriate, cooling blankets, and other supportive measures are also important.

Medical management targets multiple steps in thyroid hormone production and action to quell thyroid storm. The first order of business is to inhibit synthesis of new thyroid hormone by prescribing a thioamide. Dr. Mayer favors propylthiouracil over methimazole for this purpose because, not only does it block the thyroid gland from synthesizing new hormone, it also reduces conversion of T4 to T3. Propylthiouracil is usually given orally as a 500- to 1,000-mg loading dose, then 250 mg every 4 hours. The drug can also be given rectally or by nasogastric tube.

One hour or more after starting the thioamide, inorganic iodine is started to inhibit release of preformed hormone from the thyroid gland. Five drops of saturated solution of potassium iodide given every 6 hours is the recommended dose; it provides 764 mg of iodide per day. Lugol's solution dosed at four to eight drops every 6-8 hours is an effective alternative.

Simultaneous with starting the patient on inorganic iodine, a low-dose beta-blocker is introduced to control adrenergic symptoms.

"Propranolol is first line because it also decreases T4 to T3 conversion and it's noncardioselective, so it's better than a cardioselective beta-blocker at reducing sympathetic tone–related symptoms, such as agitation, fever, and psychosis," the endocrinologist explained.

At the same time that propranolol at 60-80 mg is given orally every 4 hours and iodine are started, the patient is placed on glucocorticoids as another means of reducing peripheral conversion of T4 to T3. The options are intravenous hydrocortisone at 100-300 mg/day in divided doses or dexamethasone at 2 mg every 6 hours.

Aspirin and NSAIDs should be avoided as antipyretics because they can actually raise T3 and T4 levels. Acetaminophen is the right fever-lowering agent in the setting of thyroid storm.

Dr. Mayer has occasionally had to reach for one of several backup therapies. Prescribing a bile acid sequestrant – 20-30 g/day of cholestyramine or colestipol – will trap thyroid hormone in the intestine, preventing it from recirculating.

"Be careful to dose it away from the other medications," she cautioned.

Also, therapeutic plasmapheresis is effective at rapidly removing circulating thyroid hormone in patients who don't show early clinical improvement in response to multipronged medical therapy.

Dr. Mayer offered a couple of final tips to hospitalists regarding thyroid storm: Know who directs plasmapheresis at your hospital, and keep the American Thyroid Association management guidelines handy (Thyroid. 2016 Oct;26[10]:1343-421).

She reported receiving funding from both NovoNordisk and Astra Zeneca.

Developing COVID-19 hospital protocols during the pandemic

By Thomas R. Collins
MDedge News

As hospitalists and other physicians at the University of Texas at Austin considered how to treat COVID-19 patients in the early weeks of the pandemic, one question they had to consider was: What about convalescent plasma?

All they had to go on were small case series in Ebola, SARS, and MERS and a few small, nonrandomized COVID-19 studies showing a possible benefit and minimal risk, but the evidence was only "toward the middle or bottom" of the evidence pyramid, said Johanna Busch, MD, of the department of internal medicine at Dell Medical Center at the university.

The center's COVID-19 committee asked a few of its members – infectious disease and internal medicine physicians – to analyze the literature and other factors. In the end, the committee – which meets regularly and also includes pulmonology–critical care experts, nursing experts, and others – recommended using convalescent plasma because of the evidence and the available supply. But in subsequent meetings, as the pandemic surged in the South and the supply dwindled, the committee changed its recommendation for convalescent plasma to more limited use, she said during HM20 Virtual, hosted by the Society of Hospital Medicine.

Dell's experience with the therapy is one example of how the center had to quickly develop protocols for managing a pandemic with essentially no solid evidence for treatment and a system that had never been challenged before to the same degree.

"It's all about teamwork," said W. Michael Brode, MD, of the department of internal medicine at Dell. "The interprofessional team members know their roles and have shared expectations because they have a common understanding of the protocol." It's okay to deviate from the protocol, he said, as long as the language exists to communicate these deviations.

"Maybe the approach is more important than the actual content," he said.

What Dr. Brode and Dr. Busch described was in large part a fine-tuning of communication – being available to communicate in real time and being aware of when certain specialists should be contacted – for instance, to determine at what oxygenation level internal medicine staff should get in touch with the pulmonary–critical care team.

> *"It's all about teamwork. The interprofessional team members know their roles and have shared expectations because they have a common understanding of the protocol."*

Dr. Brode said that the groundwork is laid for productive meetings, with agendas announced ahead of time and readings assigned and presenters ready with near-finished products at meeting time, "with a clear path for operationalizing it."

"We don't want people kind of riffing off the top of their heads," he said.

Committee members are encouraged to be as specific as possible when giving input into COVID-19 care decisions, he said.

"We're so used to dealing with uncertainty, but that doesn't really help when we're trying to make tough decisions," Dr. Brode said. They might be asked, "What are you going to write in your consult note template?" or "It's 1:00 a.m. and your intern's panicked and calling you – what are you going to tell them to do over the phone?"

The recommendations have to go into writing and are incorporated into the electronic medical record, a process that required some workarounds, he said. He also noted that the committee learned early on that they should assume that no one reads the e-mails – especially after being off for a period of time – so they likely won't digest updates on an email-by-email basis.

"We quickly learned," Dr. Brode said, "that this information needs to live on a Web site or [be] linked to the most up-to-date version in a cloud-sharing platform."

In a question-and-answer discussion, session viewers expressed enthusiasm for the presenters' one-page summary of protocols – much more, they said, and it could feel overwhelming.

Dr. Busch and Dr. Brode were asked how standardized order sets for COVID patients could be justified without comparison to a control group that didn't use the standard order set.

Dr. Busch responded that, while there was no controlled trial, the order sets they use have evolved based on experience.

"At the beginning, we were following every inflammatory marker known to mankind, and then we realized as we gained more experience with COVID and COVID patients that some of those markers were not really informing any of our clinical decisions," she said. "Obviously, as literature comes out we may reevaluate what goes into that standard order set and how frequently we follow labs."

Dr. Brode said the context – a pandemic – has to be considered.

"In an ideal world, we could show that the intervention is superior through a randomized fashion with a control group, but really our thought process behind it is just, what is the default?" he said. "I looked at the order sets [as] not that they're going to be dictating care, but it's really like the guardrails of what's reasonable. And when you're in the middle of a surge, what is usually reasonable and easiest is what is going to be done."

Dr. Busch and Dr. Brode reported no relevant financial relationships.

Performance status, molecular testing key to metastatic cancer prognosis

By Bruce Jancin
MDedge News

Performance status and molecular testing results are key tools in prognosticating for patients with newly diagnosed metastatic solid tumors, according to Sam Brondfield, MD, MA, an inpatient medical oncologist at the University of California, San Francisco.

Oncologists have at their fingertips a voluminous and ever-growing body of clinical trials data to draw on for prognostication. Yet many hospitalists will be surprised to learn that this wealth of information is of little value in the inpatient settings where they work, he said at HM20 Virtual, hosted by the Society of Hospital Medicine.

"The applicability of clinical trials data to hospitalized patients is generally poor. That's an important caveat to keep in mind," Dr. Brondfield said.

Enrollment in clinical trials is usually restricted to patients with a score of 0 or 1 on the Eastern Clinical Oncology Group performance status, meaning their cancer is causing minimal or no disruption to their life (see graphic). Sometimes trials will include patients with a performance status of 2 on the ECOG scale, a tool developed nearly 40 years ago, but clinical trials virtually never enroll those with an ECOG status of 3 or 4. Yet most hospitalized patients with metastatic cancer have an ECOG performance status of 3 or worse. Thus, the clinical trials outcome data are of little relevance.

"In oncology the distinction between ECOG 2 and 3 is very important," Dr. Brondfield emphasized.

When he talks about treatment options with hospitalized patients who have metastatic cancer and poor performance status – that is, ECOG 3 or 4 – he'll often say: "Assuming you feel better and can go home, that's when these clinical trial data may apply better to you."

Dr. Brondfield cautioned against quoting the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 5-year overall survival data when hospitalized patients with advanced cancer ask how long they have to live. For one thing, the national average 5-year overall survival figure is hardly an individualized assessment. Plus, oncology is a fast-moving field in which important treatment advances occur all the time, and the SEER data lag far behind. For example, when Dr. Brondfield recently looked up the current SEER 5-year survival for patients diagnosed with metastatic non–small cell lung cancer (NSCLC), the figure quoted was less than 6%, and it was drawn from data accrued in 2009-2015. That simply doesn't reflect contemporary practice.

Indeed, it's no longer true that the average survival of patients with metastatic NSCLC is less than a year. In the practice-changing KEYNOTE-189 randomized trial, which accrued participants in 2016-2017, the median overall survival of patients randomized to pembrolizumab (Keytruda) plus standard cytotoxic chemotherapy was 22 months, compared with 11 months with chemotherapy plus placebo (J Clin Oncol. 2020 May 10. doi: 10.1200/JCO.19.03136). As a result, immunotherapy with a programmed death–1 inhibitor such as pembrolizumab in combination with chemotherapy is now standard practice in patients with metastatic NSCLC without targetable mutations.

Performance status guides treatment decision-making

Hospitalists can help oncologists in decision-making regarding whether to offer palliative systemic therapy to patients with advanced metastatic cancer and poor performance status by determining whether that status is caused by the cancer itself or some other cause that's not easily reversible, such as liver failure.

Take, for example, the inpatient with advanced SCLC. This is an aggressive and chemosensitive cancer. Dr. Brondfield said he is among many medical oncologists who are convinced that, if poor performance status in a patient with advanced SCLC is caused by the cancer itself, prompt initiation of inpatient chemotherapy should be recommended to elicit a response that improves quality of life and performance status in the short term. If, on the other hand, the poor performance status is caused by organ failure or some other issue that can't easily be improved, hospice may be more appropriate.

"The contour of SCLC over time is that despite its treatment responsiveness it inevitably recurs. But with chemotherapy you can give people in this situation months of quality time, so we generally try to treat these sorts of patients," Dr. Brondfield explained.

The National Comprehensive Cancer Network guidelines upon which oncologists rely leave lots of room for interpretation regarding the appropriateness of inpatient chemotherapy in patients with advanced cancer and poor patient performance status. Citing "knowledge that's been passed down across oncology generations," Dr. Brondfield said he and many of his colleagues believe early palliative supportive care rather than systemic cytotoxic cancer-directed therapy is appropriate for patients with poor performance status who have one of several specific relatively nonchemoresponsive types of metastatic cancer. These include esophageal, gastric, and head and neck cancers.

On the other hand, advanced SCLC isn't the only type of metastatic cancer that's so chemosensitive that he and many other oncologists believe aggressive chemotherapy should be offered even in the face of poor patient performance status attributable to the cancer itself.

Take, for example, colorectal cancer with no more than five metastases to the lung or liver, provided those metastases are treatable with resection or radiation. "Those patients are actually curable at a high rate. They have about a 30%-40% cure rate. So those patients, even if they have poor performance status, if we can get them up for surgery or radiation, we usually do try to treat them aggressively," Dr. Brondfield said.

There are other often chemoresponsive metastatic cancers for which oncologists frequently recommend aggressive treatment to improve quality of life in patients with poor performance status. These cancers include aggressive lymphomas, which are actually often curable; multiple myeloma; testicular and germ cell cancers; NSCLC with a targetable mutation, which is often responsive to oral medications; and prostate and well-differentiated thyroid cancers, which can usually be treated with hormone- or iodine-based therapies rather than more toxic intravenous cytotoxic chemotherapy.

The impact of inpatient palliative chemotherapy in patients with poor performance status and advanced solid cancers not on the short list of highly chemosensitive cancers has not been well studied. A recent retrospective study of 228 such patients who received inpatient palliative chemotherapy at a large Brazilian academic medical center provided little reason for enthusiasm regarding the practice. Survival was short, with 30- and 60-day survival rates of 56% and 39%, respectively. Plus, 30% of patients

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ECOG performance status

Grade	Description of patient
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Source: Eastern Clinical Oncology Group

Population health can improve postdischarge care

By Thomas R. Collins
MDedge News

With the United States spending the most per capita on health care among industrialized nations but having the worst aggregate health outcomes, there's a stark need for improvement, according to an expert at HM20 Virtual, hosted by the Society of Hospital Medicine.

Broadening the focus beyond the four walls of the hospital can bring better results while also saving money, said Adam Myers, MD, chief of population health at Cleveland Clinic. Dr. Myers described the way his health system has begun to pay more careful attention to the needs of specific kinds of patients and tailoring posthospitalization care accordingly, with in-person and virtual home visits, and postdischarge clinics.

With an increasing attention to value, health care organizations have to change their structure or risk going the way of the Choluteca Bridge in Honduras, Dr. Myers said. The Choluteca Bridge was built to be hurricane proof, but was nonetheless rendered useless in 1998 after Hurricane Mitch shifted the very course of the river beneath it.

Similarly, the way health care is delivered often does not meet the needs of the population.

"Our national system has been focused almost entirely on inpatient care," Dr. Myers said. "A lot of the transition in care is outside of facilities and outside the walls of our inpatient settings."

Instead, he said a focus on population health – understanding and tending to the needs of people rather than just treating them when they show up at clinics – should involve more outpatient care that is less centralized, fees based on outcomes and patient experience rather than simply volume of services, team approaches rather than single-provider care, and a general attention to preserving health rather than treating sickness.

At Cleveland Clinic, care teams try to understand not just the care that is medically necessary, but what is wanted and justified, as well as how to deliver that care safely, reliably, and affordably with outcomes that patients and families desire.


Dr. Myers

The results are striking. After increasing the number of ambulatory patient "touches" for those with chronic disease, inpatient care – disliked by patients and costly to health centers – decreased. From the first quarter of 2018, outpatient visits increased 9%, while inpatient visits dropped 7.4%, Dr. Myers said.

"As we managed patients more effectively on an outpatient basis, their need for inpatient care diminished," he said. "It works."

Cleveland Clinic has also made changes designed to reduce costly readmissions, using virtual visits, house calls, time reserved for team meetings to identify patients with gaps in their care, and attention to nonmedical determinants of health, such as assessing fall risk at home and addressing lack of nutritious food options in a community.

The health system has seen a 28% reduction in the cost of care attributed to house calls, 12% cost reduction attributed to better care coordination, and a 49% decrease in hospital days for "superutilizers" of the ED, Dr. Myers said.

Postdischarge clinics – where patients can be seen for the first few visits after hospitalization – have also been valuable for many health systems, because they are closely in tune with what happened during the inpatient stay. These clinics are staffed by hospitalists, interns, residents, or ambulatory clinicians. Dr. Myers said hospitalists tend to have an improved perspective after working in a discharge clinic, with more concern about a patient's needs once they leave the hospital bed.

"Those hospitalists that I know who have participated in programs like this start to act a bit more like primary care physicians," he said.

In a Q&A session after Dr. Myers' presentation, he discussed how hospitalists can affect the many layers of health care policy, factors that often overlap with population health.

He noted that medical care accounts for only about 20% of patient outcomes – the rest involve social and environmental factors.

"I don't know about you , but I'm not satisfied only impacting 20% of health outcomes," he said. First, physicians need to understand what is happening in their communities, and the health policies that are preventing improvement. Then, build partnerships to help fix these problems. He pointed to lead poisoning as an example.

"If you think about it, lead poisoning is a social housing problem that shows up as a health care issue. Unless we are getting out into the community and mitigating the root problem, we will have to treat it over and over again," he said.

Dr. Myers reported no relevant financial disclosures.

Continued from previous page

were admitted to the ICU, where they received aggressive and costly end-of-life care. The investigators found these results suggestive of overprescribing of inpatient palliative chemotherapy (BMC Palliat Care. 2019 May 20;18[1]:42. doi: 10.1186/s12904-019-0427-4).

Of note, the investigators found in a multivariate analysis that an elevated bilirubin was associated with a 217% increased risk of 30-day mortality, and hypercalcemia was associated with a 119% increased risk.

"That's something to take into account when these decisions are being made," Dr. Brondfield advised.

In response to an audience comment that oncologists often seem overly optimistic about prognosis, Dr. Brondfield observed, "I think it's very common for there to be a disagreement between the oncologist wanting to be aggressive for a sick inpatient and the hospitalist or generalist provider thinking: 'This person looks way too sick for chemotherapy.' "

For this reason he is a firm believer in having multidisciplinary conversations regarding prognosis in challenging situations involving hospitalized patients with advanced cancer. An oncologist can bring to such discussions a detailed understanding of clinical trial and molecular data as well as information about the patient's response to the first round of therapy. But lots of other factors are relevant to prognosis, including nutritional status, comorbidities, and the intuitive eyeball test of how a patient might do. The patient's family, primary care provider, oncologist, the hospitalist, and the palliative care team will have perspectives of their own.

Molecular testing is now the norm in metastatic cancers

These days oncologists order molecular testing for most patients with metastatic carcinomas to determine eligibility for targeted therapy, suitability for participation in clinical trials, prognostication, and/or assistance in determining the site of origin if that's unclear.

A single-pass fine-needle aspiration biopsy doesn't provide enough tissue for molecular testing. It's therefore important to order initially a multipass fine-needle aspiration to avoid the need for a repeat biopsy, which is uncomfortable for the patient and can delay diagnosis and treatment.

Dr. Brondfield advised waiting for molecular testing results to come in before trying to prognosticate in patients with a metastatic cancer for which targetable mutations might be present. Survival rates can vary substantially depending upon those test results. Take, for example, metastatic NSCLC: Just within the past year, clinical trials have been published reporting overall survival rates of 39 months in patients with treatable mutations in epidermal growth factor receptor, 42 months with anaplastic lymphoma kinase mutations, and 51 months in patients whose tumor signature features mutations in c-ros oncogene 1, as compared with 22 months with no targetable mutations in the KEYNOTE-189 trial.

"There's a lot of heterogeneity around how metastatic tumors behave and respond to therapy. Not all metastatic cancers are the same," the oncologist emphasized.

Drug allergy in the chart? Ask patients for specifics

By Thomas R. Collins
MDedge News

Paige Wickner, MD, MPH, medical director for quality and safety at Brigham and Women's Hospital and assistant professor at Harvard Medical School, both in Boston, described a scenario that might sound familiar to hospitalists.

A 72-year-old man is admitted to the hospital for a lung transplant, and has a listed allergy to "sulfa," contained in antibiotics and other medications. His medical records say his reaction was "rash."

What do you do?

The answer, Dr. Wickner said, speaking at HM20 Virtual, sponsored by the Society of Hospital Medicine, is to first ask more questions for clarification. How bad was the rash? Was it blistering? To what type of sulfa did the patient have a reaction?

These questions can help determine the next steps. For sulfa-based antibiotics, hospitalists can often desensitize patients with certain reaction characteristics using widely studied protocols to allow the patient to temporarily take a sulfa-containing medication.

The dominant message of Dr. Wickner's talk on drug allergies was to get clear details on the allergic reaction – it can help guide clinicians through a path forward, either finding an alternative drug or performing further evaluation and perhaps continuing with the drug in question if the allergy turns out not to be a major concern.

"Please, for all of your patients, take an allergy history on every listed medication; often you will be able to remove or clarify the medical record and the changes can be life saving," she said.

For instance, desensitization to sulfa for patients who've had a morbilliform rash without a fever can be done on an outpatient basis. But if the patient had hives, or became short of breath or anaphylactic, it needs to be done as an inpatient by an allergist, she said.

SPIKE MAFFORD/THINKSTOCK

The question of drug allergies is substantial. About 35% of patients have at least one listed drug allergy, with penicillin, NSAIDs, and CT contrast agents topping the list, Dr. Wickner said. Although 10% of the general population and 15% of inpatients have a listed penicillin allergy, more than 90% of listed penicillin allergies turn out not to actually be allergic, in part because penicillin allergies are often diagnosed in childhood and are frequently outgrown over time. Having a listed allergy can impact treatment, Dr. Wickner said, with alternatives not always clear-cut.

She described one patient she saw who had 62 listed drug allergies, prompting her clinicians to wonder, "what can I safely give this patient?" Physicians, she said, subject to drug allergy "alert fatigue," tend to override about 80% of allergy alerts, but this can sometimes have serious consequences.

"The best time to clarify is when a patient is healthy and well," said Dr. Wickner, not when they are an inpatient and sick. It is much more difficult to test for an allergy, and to treat an allergic reaction, than when someone's health is quickly declining.

She urged physicians to ask patients to be specific about the name of a drug they suspect they're allergic to, about the indications, the symptoms, and the timing – an immediate reaction is much different than a symptom that showed up days later.

"Sometimes they'll say they're allergic to penicillin, but will tell you they've taken Augmentin or amoxicillin, so you can take that allergy off the list," Dr. Wickner said.

At Brigham and Women's Hospital and Massachusetts General Hospital, Boston, physicians have developed protocols for assessing and managing suspected allergies to penicillin, aspirin and NSAIDs, and trimethoprim/sulfamethoxazole – helpful tools, she said, because the nature and context of the reaction can matter a great deal in how to respond to the listed allergy.

If someone has a reaction, and you think it might be anaphylaxis, don't spend time pondering it, Dr. Wickner said. "If that thought crosses your mind, treat it like anaphylaxis, then analyze after the fact." Most patients with anaphylaxis have some cutaneous sign, even if it's just flushing.

Dr. Wickner said that, if an allergist is available, take advantage of that. "If allergy is available in-house, utilize them. Often, skin testing and/or challenge testing can help patients receive first-line therapy."

In a question-and-answer session after her presentation, Dr. Wickner said that hospitalists "have a huge role to play" in drug allergy delabeling.

"We would love to have a more standard practice of allergy reconciliation, just like we do with medication reconciliation," she said. Asking questions to get more specifics is essential – and simply asking directly about each listed allergen is "step one, and you'll really find it's going to broaden the things that you can do for your patients."

Asked about whether reactions listed as allergies are frequently just adverse effects, Dr. Wickner said that patients who say they are frequently nauseous – rather than breaking out into a rash, for example – might not be having a true allergic reaction. After careful consideration, they might be better managed with antinausea medication than avoidance of the drug.

Dr. Wickner reported no relevant financial disclosures.

Hospitalists balance work, family as pandemic boosts stress

By Thomas R. Collins
MDedge News

In a Q&A session at HM20 Virtual, hosted by the Society of Hospital Medicine, Heather Nye, MD, PhD, SFHM, professor of medicine at the University of California, San Francisco, and David J. Alfandre, MD, MPH, associate professor of medicine at New York University Langone, discussed strategies to help hospitalists tend to their personal wellness during the COVID-19 pandemic.

The speakers described the complicated logistics and emotional and psychological strain that has come from working during the pandemic, while balancing home responsibilities and parenting. The session was an opportunity to humanize hospitalists' experience as they straddle work and family.

> *"We empathize with our patients, and we empathize with our children and what their experience is."*


Dr. Alfandre

Dr. Nye said she was still "warming up to personal wellness" because there have been so many other demands over the past several months, but that taking the time to go for walks – to bring on a feeling of health even more than the physical benefits – has been helpful. Even before the pandemic, she said, she brought a guitar to the office to take a few minutes for a hobby for which she can't seem to find uninterrupted time at home.


Dr. Nye

"Bringing a little bit of yourself into your work life goes a long way for a lot of people," she said.

Child care and odd hours always have been a challenge for hospitalists, the presenters said, and for those in academia, any "wiggle room" in the schedule is often taken up by education, administration, and research projects.

Dr. Alfandre said etching out time for yourself must be "a priority, or it won't happen." Doing so, he said, "feels indulgent but it's not. It's central to being able to do the kind of work you do when you're at the hospital, at the office, and when you're back home again."

Dr. Nye observed that, while working from home on nonclinical work, "recognizing how little I got done was a big surprise," and she had to "grow comfortable with that" and learn to live with the uncertainty about when that was going to change.

Both physicians described the emotional toll of worrying about their children if they have to continue distance learning.

Dr. Alfandre said that a shared Google calendar for his wife and him – with appointments, work obligations, children's doctor's appointments, recitals – has been helpful, removing the strain of having to remind each other. He said that there are skills used at work that hospitalists can use at home – such as not getting upset with a child for crying about a spilled drink – in the same way that a physician wouldn't get upset with a patient concerned about a test.

> *"I feel like sharing that part of our job [with] our kids helps them understand that there are very, very big problems out there."*

"We empathize with our patients, and we empathize with our children and what their experience is," he said. Similarly, seeing family members crowd around a smartphone video call to check in with a COVID-19 patient can be a helpful reminder to appreciate going home to family at the end of the day.

When her children get upset that she has to go in to work, Dr. Nye said, it has been helpful to explain that her many patients are suffering and scared and need her help.

"I feel like sharing that part of our job [with] our kids helps them understand that there are very, very big problems out there – that they don't have to know too much about and be frightened about – but [that knowledge] just gives them a little perspective."

Dr. Nye and Dr. Alfandre said they had no financial conflicts of interest.


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Heart failure: Practice-changing developments for hospitalists

By Bruce Jancin
MDedge News

A recently validated, easy-to-use calculator of predicted 7-day mortality risk in patients presenting with acute decompensated heart failure is well worth incorporating into hospitalist clinical practice, Dustin T. Smith, MD, said at HM20 Virtual, hosted by the Society of Hospital Medicine.

The risk prediction tool, called the Emergency Heart Failure Mortality Risk Grade (EHMRG), can help guide clinical decision-making as to whether a patient presenting with acute heart failure is appropriate for early discharge or should instead be admitted for inpatient monitoring and more aggressive therapy, explained Dr. Smith, a hospitalist at Emory University in Atlanta.

In addition to the EHMRG, other highlights of his wide-ranging update on recent practice-changing developments in heart failure directly relevant to hospitalists included the introduction of a simple, evidence-based tool for differentiating heart failure with preserved ejection fraction from other potential causes of unexplained dyspnea on exertion in euvolemic patients, and a study debunking what has been called the potassium repletion reflex in patients with acute heart failure undergoing diuresis.

The ACUTE study

Heart failure is an area of special interest for Dr. Smith. He has been surprised to find that virtually no hospitalists, emergency medicine physicians, or cardiologists he has spoken with have heard of the EHMRG or its validation in the ACUTE (Acute Congestive Heart Failure Urgent Care Evaluation) study. Yet this is a very handy tool for hospitalists, he observed.

The EHMRG algorithm utilizes nine variables for which data are readily available for every patient who arrives at the emergency department with acute heart failure. The variables are age, arrival by ambulance, heart rate, systolic blood pressure, potassium level, oxygen saturation, troponin, serum creatine, and presence or absence of active cancer. The information is entered into a cell phone app, which spits out the patient's estimated 7-day mortality risk. The algorithm divides patients into one of five risk groups ranging from very low to very high. With the addition of data input as to the presence or absence of ST-segment depression on the 12-lead ECG, the weighted algorithm will simultaneously generate an estimated 30-day mortality risk.

ACUTE was a prospective, observational, real-world validation study of EHMRG involving 1,983 patients seeking emergency department care for acute heart failure at nine Canadian hospitals. The actual 7-day mortality rate was 0% in the very-low-risk group, 0% in the low-risk group, 0.6% with an intermediate-risk EHMRG, 1.9% with high risk, and 3.9% in the very-high-risk group. The corresponding 30-day mortality rates were 0%, 1.9%, 3.9%, 5.9%, and 14.3%.

The University of Toronto investigators also asked participating physicians for their clinical estimates of 7-day mortality risk while blinded to the EHMRG predictions. The algorithm proved more accurate than physician predictions across the board. Indeed, physicians consistently overestimated the mortality risk for all categories except the very-high-risk one, where they underestimated the true risk (Circulation. 2019 Feb 26;139[9]:1146-56).


Dr. Smith

"I'm sure you've all written orders to keep the potassium greater than 4.0 mEq/L and the magnesium above 2 mEq/L about a million times, like I have."

Given that heart failure remains year after year at the top of the list of most frequent causes for hospital admission, and that there is compelling evidence that many low-risk patients get hospitalized while potentially unsafe early discharges also occur, the EHMRG score fills an important unmet need.

"I think this can help inform us as to who with acute heart failure potentially needs to come into the hospital and who doesn't," Dr. Smith said. "I think the sweet spot here is that, if you're in the low- or very-low-risk category, your 7-day mortality is less than 1%; in fact, in this study it's zero. But once you get to category 3 – the intermediate category – you're talking about a 7-day mortality of 1%-2%, which I think is high enough to warrant hospital admission for treatment and to watch them, not just send them home."

The H2FPEF score

Diagnosis of heart failure with preserved ejection fraction (HFpEF) is a challenge in euvolemic patients with clear lungs and dyspnea on exertion. Investigators at the Mayo Clinic have developed and subsequently validated a weighted score known as the H2FPEF score that's of great assistance in this task. The score is based upon a set of six simple variables universally available in patients undergoing diagnostic work-up for the numerous potential causes for dyspnea on exertion. Together these six variables comprise the acronym H2FPEF:

- **Heavy:** One point for a body mass index greater than 30 kg/m$^{2.}$
- **Hypertension:** One point for being on two or more antihypertensive drugs.
- **Atrial fibrillation:** Three points for paroxysmal or persistent AF.
- **Pulmonary hypertension:** One point for having a Doppler echocardiographic estimated pulmonary artery systolic pressure greater than 35 mm Hg.
- **Elder:** One point for age greater than 60 years.
- **Filling pressure:** One point for a Doppler echocardiographic E/e' ratio above 9.

The total score can range from 0 to 9 (Circulation. 2018 Aug 28;138[9]:861-70).

Each 1-point increase in the score essentially doubled a patient's risk of having HFpEF as opposed to pulmonary embolism or some other cause for the dyspnea.

"I really like this H2FPEF score. The score works very, very well. Once you get to a score of 6 or above, the probability of HFpEF is more than 90%, which is pretty powerful. I think this is worthwhile," Dr. Smith said.

In their derivation and validation cohorts, the Mayo Clinic investigators used as their gold standard for diagnosis of HFpEF invasive hemodynamic exercise testing with a pulmonary artery catheter in place to measure pressures. A score that enables hospitalists to lessen the need for that kind of costly invasive testing is most welcome.

"Here's how I'd use this score: With an H2FPEF score of 0-1, HFpEF is unlikely. With an intermediate score of 2-5, additional testing is warranted. If the score is high, 6-9, I think HFpEF is likely," the hospitalist said.

Dr. Smith isn't the only big fan of the H2FPEF score. In an editorial accompanying publication of the score's validation study, Walter J. Paulus, MD, PhD, hailed the H2FPEF score as "a unique tour de force" which constitutes a major advance beyond the confusing diagnostic recommendations for HFpEF issued by the European Society of Cardiology and the American Society of Echocardiography, which he said have been "met by skepticism qualifying them as overcomplicated and even triggered disbelief in the existence of HFpEF."

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Managing acute pain in inpatients on OUD therapy

By Bruce Jancin
MDedge News

As the opioid epidemic rolls on, hospitalists can expect to increasingly encounter the challenge of treating acute pain in inpatients on medication-assisted treatment for opioid use disorder.

"This is something we're going to see more frequently, and many of us already have," Theresa E. Vettese, MD, said at HM20 Virtual, hosted by the Society of Hospital Medicine.

The drastic drop in prescriptions for opioid pain medications in the last several years hasn't curtailed the current opioid epidemic. Instead, the epidemic has to a great extent morphed into expanded use of illicit heroin and fentanyl, noted Dr. Vettese, an internist, hospitalist, and palliative care physician at Emory University and Grady Memorial Hospital in Atlanta.

Mythbusting

Treatment of acute pain in hospitalized patients on opioid agonist therapy for opioid use disorder (OUD) is actually pretty straightforward once a few common myths have been dispelled, she said.

One of these myths –common among both physicians and patients in treatment for OUD – is that prescribing opioids for management of acute pain will place such patients at risk for OUD relapse.

"In fact, the data really strongly suggest this is not the case," Dr. Vettese said. "It will not worsen addiction. But if we don't aggressively treat these patients' acute pain, it puts them at higher risk for bad outcomes."

Another myth – this one not uncommon among hospital pharmacy departments – is that only physicians with a special certification can prescribe methadone for inpatients.

"The federal laws are clear: Any physician who has a DEA license can prescribe methadone in the hospital acute care setting, not only for pain management, but also for treatment of opioid withdrawal. You can't prescribe it in the outpatient setting for opioid withdrawal – that has to be dispensed through a federally regulated methadone outpatient treatment program. But in the hospital, we can feel safe that we can do so. You may need to educate your pharmacist about this," she said.

Hospitalists also can prescribe buprenorphine in the acute care inpatient setting, both for pain and treatment of opioid withdrawal, without need for a DEA waiver.

"It's useful to get some skills in using buprenorphine in the inpatient setting. You don't need an X waiver, but I encourage everyone to do the X-waiver training because it's a terrific educational session. It's 8 hours for physicians and well worth it," Dr. Vettese noted.

By federal law the inpatient physician also can prescribe 3 days of buprenorphine at discharge to get the patient to an outpatient provider.

Misconceptions also abound about NSAIDs as a nonopioid component of acute pain management in hospitalized patients. They actually are extremely effective for the treatment of musculoskeletal,


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orthopedic, procedural, migraine, and some types of cancer pain. The number needed to treat (NNT) for postoperative pain relief for ibuprofen or celecoxib is 2.5, and when used in conjunction with acetaminophen at 325 mg every 4 hours, that NNT drops to 1.5, similar to the NNT of 1.7 for oxycodone at 15 mg. It should be noted, however, that the bar defining effective pain relief in randomized studies is set rather low: a 50% greater reduction in pain than achieved with placebo.

Many hospitalists would like to use NSAIDs more often, but they're leery of the associated risks of GI bleeding, ischemic cardiovascular events, and worsening kidney function. Dr. Vettese offered several risk-mitigation strategies to increase the use of NSAIDs as opioid-sparing agents for acute pain management.

She has changed her own clinical practice with regard to using NSAIDs in patients with chronic kidney disease in response to a 2019 systematic review by investigators at the University of Ottawa (Curr Opin Nephrol Hypertens. 2019 Mar;28[2]:163-70).

"This was a game changer for me because in this review, low-dose NSAIDs were safe in that they didn't significantly increase the risk of worsening kidney failure even in patients with stage 3 chronic kidney disease. So this has expanded my use of NSAIDs in this population through stage 3 CKD. With a creatinine clearance below 30, however, kidney failure worsened rapidly, so I don't do it in patients with CKD stage 4," Dr. Vettese said.

Gastroenterologists categorize patients as being at high risk of GI bleeding related to NSAID use if they have a history of a complicated ulcer or they have at least three of the following risk factors: age above 65 years, history of an uncomplicated ulcer, being on high-dose NSAID therapy, or concurrent use of aspirin, glucocorticoids, or anticoagulants. Patients are considered at moderate risk if they have one or two of the risk factors, and low risk

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Particularly interesting were the variables rejected for inclusion in the H2FPEF score because they failed to achieve statistical significance as predictors, even though they're often considered important in defining HFpEF, he noted. These included left atrial volume index, sex, and levels of circulating N-terminal probrain natriuretic peptide, wrote Dr. Paulus, professor of cardiac pathophysiology at VU University, Amsterdam.

Debunking the potassium repletion reflex

Longstanding conventional wisdom holds that patients hospitalized for heart failure need to maintain a serum potassium above 4.0 mEq/L.

"I'm sure you've all written orders to keep the potassium greater than 4.0 mEq/L and the magnesium above 2mEq/L about a million times, like I have," Dr. Smith said.

But it turns out this traditional practice, which involves a huge cost in terms of time, money, and health care resources, is supported by weak evidence – and an important recent study has now debunked what the investigators termed the potassium "repletion reflex."

The investigators at the University of Massachusetts identified 4,995 patients admitted with exacerbation of acute heart failure and a normal admission serum potassium level of 3.5-5.0 mEq/L. More than 70% received potassium repletion at least once within a 72-hour observation window, during which 2,080 patients maintained a low-normal serum potassium below 4.0 mEq/L, 2,326 had a mid-normal level of 4.0-4.5 mEq/L, and 589 had a high-normal level of more than 4.5 mEq/L but not more than 5.0 mEq/L.

The study had three endpoints: in-hospital mortality, transfer to the intensive care unit, and hospital length of stay. After statistical adjustment for comorbidities, demographics, and severity at admission, there was no difference between the low- and mid-normal serum potassium groups in any of the three endpoints. In contrast, the high-normal potassium group had a significantly longer length of stay, by a median of 0.6 extra days. The high-normal group also had a 78% increased likelihood of ICU transfer and a 51% increased risk of in-hospital mortality, although neither of these differences reached statistical significance (J Hosp Med. 2019 Dec 1;14[12]:729-36).

"A potassium greater than 4.5 mEq/L may be associated with increased risk of worse outcomes," Dr. Smith observed. "I think the sweet spot may be 3.5-4.5 mEq/L based on this study."

He reported having no financial conflicts regarding his presentation.

HM20 Virtual: Improved supervision of residents

By Ann-Marie Tantoco, MD, FAAP, FHM

HM20 Virtual session title

Call Me Maybe: Balancing Resident Autonomy With Sensible Supervision

Presenter

Daniel Steinberg, MD, SFHM, FACP

Session summary

In this session, Dr. Steinberg, professor of medicine and medical education, associate chair for education, and residency program director in the department of medicine at Icahn School of Medicine at Mount Sinai, New York, presented key factors, techniques, and approaches to supervising residents. He discussed the important balance of resident autonomy and supervision, especially since attendings need to focus on learner education along with patient care and safety.

Dr. Steinberg stated that resident supervision is driven by three factors: what residents need, what residents want, and what the supervisor can provide. Although data are mixed on whether supervision improves patient outcomes, supervision is essential for patient care and resident education. Dr. Steinberg showcased several relevant medical education studies relating to supervision and focused on a key question: Do you trust the resident?

The review of medical education literature discussed the meaning and development of trust, oral case presentations to determine trust, and the influence of supervisor experience. One study looked at the attendings' remote access of EMR, which allows for remote supervision as a great way to determine trust of the resident. Another study showed that attendings want more communication than what residents provide and that the saying "Page me if you need me" does not encourage communication from residents as much as attendings would desire.

Key takeaways

- Resident supervision is driven by what residents need, what residents want, and what the supervisor can provide.
- Trust can be determined from direct supervision, oral presentations, and remote access of EMR, but it is also influenced by attending experience and style.
- To increase resident communication with the attending, do not say "Page me if you need me." Instead, an attending should specifically state when a call to an attending is required.

Dr. Tantoco is an academic med-peds hospitalist practicing at Northwestern Memorial Hospital in Chicago and Ann & Robert H. Lurie Children's Hospital of Chicago. She is an instructor of medicine (hospital medicine) and pediatrics at Northwestern University, also in Chicago.

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if they have none. Dr. Vettese said that, while NSAIDs clearly should be avoided in the high-risk group, moderate-risk patients are a different matter.

"Many avoid the use of NSAIDs with moderate risk, but I think we can expand their use if we use the right NSAID and we use protective strategies," Dr. Vettese said.

Celecoxib is the safest drug in terms of upper GI bleeding risk, but ibuprofen is close. They are associated with a 2.2-fold increased risk of bleeding when compared with risk in patients not on an NSAID. Naproxen or indeomethacin use carries a fourfold to fivefold increased risk.

"Celecoxib with a proton pump inhibitor is safest, followed by celecoxib alone, followed by ibuprofen with a proton pump inhibitor. So I advocate using NSAIDs more frequently in people who are at moderate risk by using them with a PPI," she said.

There is persuasive evidence of increased cardiovascular risk in association with even short-duration NSAIDs, as the drugs are utilized in the treatment of acute pain in hospitalized patients. That being said, Dr. Vettese believes hospitalists can use these drugs safely in more patients by following a thoughtful cardiovascular risk-mitigation strategy developed by Italian investigators (Ther Adv Drug Saf. 2017 Jun;8[6]:173-82).

Communicating about pain management

"Communication is always the key to effective pain management in every situation," Dr. Vettese emphasized.

"I talk to the patient about the goals of effective pain management. I'll discourage the use of the 1-10 pain scale, and instead, I'll be honest about expectations, saying, 'You have a problem that will cause acute pain, and it's unlikely that I will be able to completely relieve your pain. The goal is to improve your function so that you can get up and go the bathroom by yourself, and so that you can sleep for a few hours. That's how we're going to measure the efficacy of our pain-management program.'"

She explains to the patient that she'll be using nonopioid medications and nondrug therapies along with oral opioid pain medications, which are less risky than IV opioids. She offers reassurance that this treatment strategy won't cause an OUD relapse. She lets the patient know up-front that the opioids will be tapered as the acute pain improves.

For the patient who comes into the hospital on buprenorphine for OUD, she immediately checks with the state prescription drug monitoring program to make sure everything is above board and there's no indication of doctor shopping for prescriptions. For in-hospital acute pain, it's safe and effective to continue the outpatient dose. On an outpatient basis, however, the drug is given once daily. On that dosing schedule both the euphoric effect as well as the analgesic effect are lost, so for acute pain management in the hospital it's recommended to split the dose into twice- or thrice-daily doses to achieve an analgesic effect.

> *"Many avoid the use of NSAIDs with moderate risk, but I think we can expand their use if we use the right NSAID and we use protective strategies."*

Oral NSAIDs are part of the treatment strategy whenever possible. For severe acute pain, Dr. Vettese will prescribe an immediate-release opioid having a high affinity to the mu opioid receptor, such as oral hydromorphone, on an as-needed basis. The drug has onset of effect in 30 minutes, peak effect in 1 hour, and a duration of effect of 4-6 hours, although she recommends going with 4 hours to provide adequate analgesia.

"These patients will require much higher doses than the patients who are opioid naive," she advised.

For the patient with acute pain who is admitted while on methadone for OUD, it's important to call the outpatient treatment program to verify the dosage.

"You can split the dose of methadone to try to get better analgesia, although I can tell you that patients who are treated with methadone for OUD frequently don't want to do that. And if they don't want to, then I don't," the hospitalist said.

As with the patient on buprenorphine for OUD, she'll use additional oral immediate-release opioids as needed for acute severe pain in a patient on methadone for medication-assisted OUD treatment.

Dr. Vettese reported having no financial conflicts regarding her presentation.

The Future Hospitalist

A strong mentor/mentee relationship

Establish clear expectations from the beginning

By Jessica Zimmerberg-Helms, MD, and Patrick Rendon, MD

I. Finding a mentor

Case

You are a 27-year-old first-year resident who is seeking mentorship. You are halfway through the year and are thinking about your goals and future. You have a general interest in hematology/oncology but have limited experience and would like to gain more experience with clinically relevant scholarship. However, you do not know anyone in the field and are not sure who to ask for guidance.

Stage 1: Seeking the right mentor

Start first with your area of interest and then look broadly. In this case the resident is interested in heme/onc. The first place to look is on the heme/onc department website or in the faculty directory. It can be helpful to look at what the potential mentor has published recently and/or look at a version of their CV on the faculty directory or website. This can help determine how productive they are and help assess whether you share similar interests, and whether they have worked with many learners in the past.

It is also important to do some background work and ask around about potential mentors. Often resident colleagues and fellows have a good sense of current projects and which faculty work well with learners. Lastly, it is important to also look at non–heme/onc physicians as there may be internal medicine physicians or surgeons who are doing hematology or oncology research that more align with your interests.

After you have assessed whether you think this person would be a strong mentor for you, it is time to reach out. People are flattered to be asked and part of their promotion criteria is their ability to mentor. Do not assume that a potential mentor is too busy! Let him or her make that decision. Remember the worst a mentor can say is "no." Even if they do not have time or the need for a mentee at the present time, they generally will offer some assistance or direction on who to ask.

Start with a straightforward, but pleasant email. Waiting up to 2 weeks for a response is reasonable. If after 2 weeks you have not received word, feel free to reach out again asking politely if he or she would be willing to work with you. Do not be afraid to ask bluntly for their guidance and mentorship and have a specific project or area of research that you would like their assistance with.

II. Optimizing the mentor/mentee relationship

Case continued

Success! Your email was received with interest by a hematologist who has done several projects, comes highly recommended by other residents, and worked with students and residents in the past. The project involves anticoagulation on the inpatient service. You are set to meet with her next month.

Stage 2: Establishing expectations and goals

Now comes the hard work in establishing an excellent mentor/mentee relationship. Before you meet with your mentor, brainstorm first. What do you want out of the relationship? A publication? Career advice? A fellowship position? You should feel empowered in knowing that you as the mentee are in the driver seat, but this relationship should be mutually beneficial. Consider basing the relationship and initial discussions on these key questions:

1. My goals

- What are my goals? It is okay not to know but be ready to communicate some information to your mentor.
- Remember to also ask your mentor what their goals are for you as well.

2. Outcome

- What type of outcome are both you and your mentor looking for from the relationship?

3. Expectations

- What mentorship expectations do you have?
- What are your mentor's expectations of you?

Once you feel you have a sense of what you are looking for out of the relationship, it is important to communicate this with the mentor to establish congruent expectations of one another. For example, think about asking your mentor if the two of you can establish a mentor/mentee contract. This is a written document that can be found online and establishes a mutual agreement of roles, responsibilities, and expectations of one another for the relationship. It can further help to open a line for honest and consistent feedback. This can also give you a formalized endpoint and agreed-upon scope for the mentoring relationship. Having a check-in preestablished in a contract reduces any potentially awkward conversations about redefining the relationship down the road. (For example, what if our case resident decides to pursue GI? It could happen.)

Stage 3: Establishing a common goal

After you have determined the goals and expectations of the relationship together (remember, this is a relationship), it is time to start exploring possible projects and establishing goals for those projects. Having a quality improvement or research project will determine a common goal to work toward and help establish and define the relationship.

Once you have delineated broadly what the project(s) should be, develop smaller SMART (specific, measurable, achievable, relevant, time-bound) goals to move the project forward. These goals determine stopping points for evaluation and feedback, which further establish the relationship and keep the project(s) progressing. For example, one goal could be to write the first draft of the proposal for your quality improvement project within 3 weeks.

Dr. Zimmerberg-Helms

Dr. Rendon

Dr. Zimmerberg-Helms is a resident physician at the University of New Mexico, Albuquerque. Dr. Rendon is an attending hospitalist at the University of New Mexico.

Stage 4: Continuing communication

With any project it is important to stay on the same page as your mentor and be clear to establish "who is doing what by when." Do not expect accountability to be the mentor's job. Remember that you are in the driver's seat and that you should propose how often you need to meet and what those meetings look like by developing an agenda. You can have an open discussion and allow your mentor to help determine a reasonable timeline. Remember, the more you communicate your goals, the better your mentor will be able to address them.

One pro tip is to always exceed your mentor's expectations – if you think you need 2 weeks to complete a task, ask for 3-4 weeks. This gives you extra padding in case of unforeseen circumstances and makes you look like a "rockstar" if you hit a deadline 1-2 weeks earlier than planned.

III. Ending and/or redefining the relationship

Case continued

You are now a senior resident who's published multiple articles in the past year, and have completed an anticoagulation project for inpatients with pulmonary emboli. You look back on your experience and what stands out is the extent of your gratitude and appreciation for your incredible mentor. Not only do you feel that your mentor has guided you in your career and with your scholarship, but you feel that he or she has shaped your character and talent set. At this point your mentor is both a teacher and guide, but now also a friend. While you feel there is always more that you can learn from her, you are ready to explore new interests. How do you effectively end or redefine this relationship?

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HM20 Virtual

Key takeaways for the pediatric hospitalist

By Anika Kumar, MD, FHM, FAAP; Vignesh Doraiswamy, MD; Ann-Marie Tantoco, MD, FHM, FAAP

The HM20 Virtual conference in August was filled with excellent content that can be applied by all hospitalists. This article summarizes some key concepts and takeaways for the pediatric hospitalist.

Racism and bias in medicine

HM20 Virtual session: Structural Racism and Bias in Hospital Medicine During Two Pandemics
Presenters: Nathan Chomilo, MD, FAAP; and Benji K. Mathews, MD, SFHM

Dr. Chomilo, of HealthPartners in Minneapolis, explained how racial disparities are a symptom of racism. The presenters showed how structural racism has been propagated in medicine with the Hospital Survey and Construction Act of 1964 that allowed segregated hospitals, as well as the racism that exists within the "hidden curriculum."

Dr. Chomilo discussed how personal experiences of racism can lead to worse health outcomes, including depression, obesity, and overall poor health. Dr. Mathews, also of HealthPartners, explained how implicit biases can be addressed at the individual level, the organizational level, and simultaneously at both to create an antiracist culture. He presented strategies to mitigate individual biases; recognize when biases may be triggered; check biases at the door; connect with others from different backgrounds as equals; and practice antiracism by being an active bystander. Dr. Chomilo concluded the session by sharing that we can all grow by addressing racism at "our houses" (health care systems, medical schools, payer systems) with the goal to create an antiracist system.

Key takeaways

- Racial disparities are a symptom of structural racism that has been propagated in medicine for centuries.
- Addressing implicit biases at the individual level, organization level, and simultaneously at both levels can help leaders model and promote an antiracism culture.

HM20 Virtual session: When Grief and Crises Intersect: Perspectives of a Black Physician in the Time of Two Pandemics
Presenter: Kimberly Manning, MD, FACP, FAAP

Dr. Manning, of Emory University in Atlanta, discussed the dual pandemics of COVID-19 and the racism that we are currently experiencing, and described the unique perspective of Black Americans. Though it is easy to see that COVID-19 is a pandemic, racism is not always seen in this way. Dr. Manning demonstrated that, when a pandemic is defined as "that which occurs over a wide geographic area and affects a high proportion of the population," racism is absolutely a pandemic. Black Americans have been disproportionately affected by COVID-19. Dr. Manning said we often hear that we are in "unprecedented times" but as far as racism is concerned, there is nothing new about this. She shared stories of personal milestones; but each of these instances, though marked by beauty, was also marked by something truly awful. Each time she had a reason to smile, there was something awful going on in the country that showed how racism was still present. Dr. Manning said that, though these were her stories, all Black Americans can recount the same stories, emotions, and feelings of grief.

Dr. Manning concluded by sharing how we can "Do The Work" to combat the pandemic of racism: broaden our funds of knowledge, remember that people are grieving, explore our implicit biases, be brave bystanders, and avoid performative allyship.


Dr. Kumar


Dr. Doraiswamy


Dr. Tantoco

Dr. Kumar is the pediatric editor of The Hospitalist. She is clinical assistant professor of pediatrics at the Cleveland Clinic Lerner College of Medicine at Case Western Reserve University and a pediatric hospitalist at Cleveland Clinic Children's. Dr. Doraiswamy is an assistant professor of medicine and pediatrics and a med-peds hospitalist at The Ohio State University and Nationwide Children's Hospital, both in Columbus. Dr. Tantoco is an academic med-peds hospitalist practicing in Northwestern Memorial Hospital, Chicago, and Ann & Robert H. Lurie Children's Hospital of Chicago.

Key takeaways

- Though the COVID-19 pandemic is unprecedented, the pandemic of racism is not.
- We must "Do The Work" to combat everyday racism and to be cognizant of what our Black colleagues are going through every day.

Immigrant hospitalist challenges

HM20 Virtual session: The Immigrant Hospitalist: Navigating the Uncertain Terrain During COVID-19
Presenters: Manpreet S. Malik, MD, FHM; and Benji K. Mathews, MD, SFHM

Dr. Malik of Emory University in Atlanta, and Dr. Mathews of HealthPartners, opened this session by sharing their personal stories as immigrant physicians in the United States. Dr. Malik noted that physicians born outside the United States make up 29% of U.S. physicians, and 32% of hospitalists are international medical graduates.

The presenters revealed the structural hurdles immigrant physicians face, including lack of empowerment until achieving permanent residency status; limited leadership, administrative, and academic roles; concerns for job security and financial stability; and experiencing micro- and macroaggressions at work. The presenters shared a framework for a developmental orientation inclined toward cultural competency beginning with denial, followed by polarization, progressing to minimization, advancing to acceptance, and culminating in adaptation.

They concluded the session by stressing the importance of advocacy for immigrant physicians and encouraged colleagues to become engaged in efforts within their professional organizations.

Key takeaway

- Immigrant physicians experience structural challenges to their professional advancement because of their residency status.

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Stage 5: Redefining your mentoring relationship
First, go back to the expectations or contract established early in the relationship. The check-in is a key time in the relationship to reevaluate goals and priorities. At this point you may decide to amicably end the relationship or project, or move on to a new project with a change in your role. For example, the quality improvement project may change to research, or you as the mentee have a change in focus (e.g., change in specialty or scholarly focus).

In summary, the interaction between you and your mentor should be a relationship. And the keys to a great relationship are:

1. Establish clear expectations from the beginning. This clarifies the relationship and helps the mentee and mentor to become more successful.

2. Maintain clear and open communication throughout the relationship.

3. Define your goals and discuss them with your mentor early. (Have we mentioned the importance of goals enough?) After all, your goal is the reason you started pursuing this relationship in the first place.

In clinical training having guidance can greatly enhance your experience and direct your future career in unexpected ways. We hope that using these tools will guide you toward forging a strong mentor/mentee relationship.

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