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FROM THE EDITOR'S DESK

The Magic Potion Is Staying in Motion

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Editor in Chief

In July, President Donald Trump issued an executive order to emphasize fitness in U.S. schools.[1] He and Secretary of Health and Human Services Robert F. Kennedy, Jr. have suggested we bring back the Presidential Fitness Test. This program was originally created by President Dwight D. Eisenhower in the 1950s, and in fact, this continued emphasis on physical education should be lauded, as multicomponent goal-directed interventions to increase exercise likely improve participation and lead to positive, measurable long-term health outcomes.[2]

To be clear, our leaders should extend their vision to support adequate and quality nutrition interventions as well, rather than, for example, reducing SNAP-funded free and reduced-price lunches. Yet, few would argue that continued emphasis on physical education is negative. We are in the midst of an obesity epidemic with well-known adverse implications, and the prohibitive costs and risks associated with weight-loss medications reassure us that lifestyle interventions are still necessary, even vital.

At the same time, advice regarding diet alone to improve health is not sufficient. A literature review reveals that an emphasis by physicians to improve fruit and vegetable consumption has only marginal effect on actual intake and probably no meaningful impact on overall health.[3]

How valuable is exercise? Let's set aside the obvious benefit that a physically active lifestyle can have on almost every chronic orthopedic and rheumatologic disorder. Cardiac rehabilitation is recommended for almost every patient who has had a cardiac event or intervention.[4] In addition, exercise improves atrial fibrillation recurrence, symptom burden and severity, as well as the mental components of quality of life.[5]

In people with pulmonary hypertension, exercise programs increase exercise capacity, pulmonary arterial pressure, and quality of life.[6] Exercise prescriptions for older individuals can reduce the rate of falls and the number of people who fall.[7] Exercise improves walking distance and pain in people living with claudication.[8] It significantly improves sugar control, visceral adipose tissue, and plasma triglycerides in people with type 2 diabetes, even if they do not lose weight.[9] Pulmonary rehabilitation results in meaningful improvements in functional exercise capacity and quality of life in adults with asthma and improves exercise capacity and quality of life in people with COPD.[10,11]

In the realm of mental health and neurology, study results indicate that exercise has positive short-term effects on self-esteem in children and mental health scores among pediatric patients with anxiety and depression.[12,13] In addition, exercise is moderately more effective than control for reducing symptoms of depression in adults.[14] Physical exercise improves functional capacity and reduces pain scores in all comers with chronic pain, and improves many parameters of health in cancer survivors, including fatigue and depression.[15-17]

Study results further indicate that regular exercise programs have positive effects on both the physical and mental health of individuals with schizophrenia.[18] Additionally, physical activity likely has beneficial effects on the severity of motor signs as well as quality of life for people living with Parkinson's disease, although, as in most studies, it is not clear what, if any, is the best type of exercise to achieve these benefits.[19]

Exercise, performed for about 45 to 60 minutes each time, three times per week or more, regardless of intensity, may also provide a clinically significant reduction in menstrual pain intensity,[20] and it helps avert bone loss in postmenopausal women.[21] Further, exercise reduces the risks of developing gestational diabetes and having a caesarean section when combined with diet interventions during pregnancy.[22]

Being physically active reduces the severity of symptoms and the number of symptom days among patients with acute respiratory infections,[23] and it improves symptoms in people diagnosed with irritable bowel syndrome.[24] Finally, prehabilitation may result in improved symptoms preoperatively and postoperatively in patients who will undergo colorectal procedures, and physical interventions and multidisciplinary interventions increase the likelihood that people with cancer can return to work.[25,26]

The American College of Sports Medicine offers recommendations about how to write exercise prescriptions,[27] but based on the results of much of the literature, recommendations do not need to be terribly specific. In truth, people exercise for different reasons. Part of good history-taking reveals whether patients are competitive, exercise to be social, or because their body tells them that it needs to move. Understanding this aspect of one's character may help us advise on how to engage. We as clinicians should embrace this moment of national attention to help our patients make positive change.

Studies reveal that the more frequently patients hear advice to exercise, the more likely they are to participate.[28] Thus, at the very least, Americans should be encouraged to exercise 150 minutes per week,[29] and medical education and continuing education should emphasize ways to accomplish this. In addition, physical activity level should be measured like a vital sign at every clinical encounter, and clinicians should find ways to advise regarding activity during nearly every patient encounter.

Time should be set aside for exercise every day, just as it is for sleeping, hygiene, and spiritual introspection. Thus, I applaud Mr. Trump and Mr. Kennedy for their attention to this subject and would encourage more public emphasis be placed on making environments safe and accessible for exercise. Let's continue to fund the nation's parks and even incentivize physical activity — for example, OSHA standards could stipulate space and 30-minute breaks to exercise just as we are already given the opportunity to eat.

Clearly there's more to do. Let's keep moving.

REFERENCES

Visit jlgh.org/StayInMotion or scan the QR code at left to view the references for this article.

JLGH Summer 2025 Recap

Q&A for Extended Learning

The Summer issue of The Journal of Lancaster General Hospital *offered articles on transitioning pediatric patients to adult care, vaccine-preventable pediatric illnesses and vaccine hesitancy, GLP-1 receptor agonist safety considerations, and other practice recommendations. Review the questions and answers below to see how much you remember from the issue. Need a refresher? All issues of* JLGH *are available at JLGH.org.*

Q **List tools and methods that can help pediatric patients with complex medical conditions successfully transition to adult care.**

A Implementing intentional programming, using medical workbooks to help identify goals, creating and developing a transition plan, and appointing a transition coordinator are initiatives that may help lead to a smooth and successful transition.

Q **What is the "3A" approach to help clinicians counsel patients regarding the risks and benefits of vaccines in the new era of social media myths?**

A *Avoid fear tactics* when counseling parents during a well-child visit, *ask for permission* to debunk myths in the office, and *adapt language* and key phrases to use with every family.

Q **Compounded versions of GLP-1 receptor agonists have gained popularity among consumers. How should clinicians advise patients before they purchase these products?**

A Patients should understand that compounded drugs do not undergo FDA premarket review for safety, effectiveness, or quality. Prescriptions should be filled at state-licensed compounding pharmacies using the base form of the drug obtained from FDA-registered facilities. Pharmacies should be able to ensure compounding sterility and avoid the addition of other ingredients that may cause interactions. Pharmacists should be both FDA registered and credentialed to compound.

Q **Parents should keep communication channels open and be an example regarding their children's use of electronic devices. What recommendations can clinicians offer adolescents?**

A Devices should be put away one hour before bedtime. Device features such as "Do Not Disturb" and "Notifications" should be set to control usage. Children should be encouraged to spend less time on devices to allow more time for other activities like exercising and spending time with family.

Q **Foreign bodies ingested by adults might pass through without harm, although complications may occur. Name some emergent complications and treatment options.**

A Intestinal perforation, bleeding, sepsis, compression necrosis, and obstruction are the most likely complications, especially if an object has a diameter >5 cm or a sharp edge. Endoscopy, including enteroscopy or colonoscopy, may be warranted.

Pediatric Headache in Primary Care

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A 12-year-old male presents to his primary care clinician with the chief complaint of headache. What strategies would be helpful in a busy primary care office to assess for secondary causes of headache? When should neuroimaging be considered? What are some common primary headache disorders and how are they diagnosed? What important lifestyle modifiers could be influencing headaches? What types of rescue strategies and medications should be discussed? When should prevention strategies utilizing supplements and medications be considered?

The goal of this article is to summarize important points for the primary care clinician when evaluating a child or adolescent with a complaint of headache. A helpful resource is the CHOP Primary Care Clinical Pathway for Evaluation and Management of Child with Headache, available by scanning the QR code at left.

INTRODUCTION

Headache disorders cause substantial disability worldwide in adolescents and young adults, and also have a negative impact on the quality of life of affected children and adolescents.[1,2] The prevalence of migraine disease in children 5 to 10 years old is 5% and in adolescents is as high as 15%.[1,3]

Children and adolescents with migraine disease are absent from school more than their peers, and social interactions — including those during classes and at lunch — are often limited.[4,5] Migraine disease has also been associated with comorbidities such as sleep disorders and depression and anxiety.[2] Attempted and completed suicide occurs more often in patients 15 years of age and older diagnosed with headaches as compared to those without.[6]

The primary care clinician can help many children and adolescents with headaches, as two-thirds of children and adolescents will respond to headache therapies.[7,8] For appropriate acute and prevention therapies to be offered, however, the clinician will need to conduct a thoughtful and directed evaluation.

EVALUATING FOR A SECONDARY HEADACHE

A secondary headache is a headache that is a symptom of an identifiable cause, such as an infection or intracranial lesion.[9] Life-threatening causes, such as brain tumors, occur in about 1% of children and adolescents with headaches in a primary care setting.[10,11]

It is important for the primary care clinician to assess for other secondary headaches that may affect management. It is possible for a child to have both primary and secondary headache; for example, a child with migraine disease may have a flare of migraine triggered by an upper respiratory infection.

Medical literature does promote the use of red flags to screen for secondary headache disorders, but there is a lack of epidemiologic studies regarding red flags.[11] Red flags can be defined as symptoms or signs that would suggest the need for additional evaluation or observation. The CHOP Primary Care Clinical Pathway for Evaluation and Management of Child with Headache utilizes the mnemonic SNOOPY (see Table 1 on page 69) to encourage investigators to evaluate for secondary headache; this was adapted from SNOOP10, designed to help discern the cause of secondary headache in adults.[11-13]

The absence of red flags suggests that additional evaluation, such as neuroimaging, would offer a low yield and is not indicated.[14] Parents and caregivers, however, are at times worried that a headache is a sign of a life-threatening cause. If there are no red flags and the concern for a secondary cause of the headache is low, providing reassurance can be helpful.

The presence of a red flag, or multiple red flags, should prompt the clinician to pause and consider further evaluation, such as expedited subspecialty referral

and/or neuroimaging. It is important to note, however, that a high proportion of patients who present with headache report at least one red flag, and a secondary headache disorder is more often suspected than detected.[11] Multiple studies have revealed that even with the use of red flags, neuroimaging is often unremarkable.[15-17] Findings that may offer a higher yield for a secondary headache are an abnormal neurologic exam, systemic illness, and new or worsening headache.[12]

PRIMARY HEADACHE

Primary headaches are idiopathic with no known secondary cause and diagnosed clinically based on the International Clarification of Headache Disorders (ICHD-3) diagnostic criteria. The committee that created this extensive document indicates that neuroimaging is not needed for the obvious case of migraine or tension-type headache but is useful when the diagnosis is uncertain.[18]

With the high prevalence of primary headache disorders, primary care clinicians should be familiar with some of the more common primary headaches found in children and adolescents. Migraine and tension-type headaches are the two most common primary headache disorders. Other, less common primary headache disorders in children and adolescents include new daily persistent headache, trigeminal autonomic cephalalgia, and stabbing headache.[1,12]

In most instances, answers derived from a set of headache-based questions will suggest the pattern of a primary headache disorder; headache frequency, pattern, location, quality, severity, as well as associated features, should all be ascertained.[12,19] As a rule of thumb, migraine is a headache with associated symptoms, while tension-type headache is a headache without associated symptoms.

Migraine

Frequent migraines can be disabling and often have a negative impact on the individual's quality of life — this should not be underestimated or overlooked. Children and adolescents with migraine disease have lower quality-of-life scores on the Pediatric Quality of Life Inventory, with scores similar to those of children and adolescents diagnosed with cancer and arthritis.[20]

Migraine headaches may be described as with or without aura.[18] Most children and adolescents will have migraine without aura, but about 20% will have a preceding or overlapping aura, typically visual, less commonly sensory (tingling > numbness), speech and/or language, motor, brainstem, and retinal.[18] The aura may accompany the headache and may even precede the headache by as much as 60 minutes.[18] Some may have weakness, dysarthria, and coordination difficulties; initial or prolonged presentation of these symptoms should prompt the clinician to use neuroimaging to assess for vascular pathology, such as stroke.[18]

Based on ICHD-3 criteria, migraine without aura may be diagnosed when a patient younger than 18 years has experienced at least five lifetime attacks, each with a duration of between 2 and 72 hours.[18,21] The headache may be unilateral or bilateral, pulsating, of moderate or severe pain intensity, and aggravated by physical activity; associated symptoms may be nausea and/or vomiting, or photophobia and phonophobia.[18]

Tension-Type Headache

Tension-type headaches are common in children and adolescents but generally considered less severe when compared to migraines. Patients often do not seek medical attention as these types of headaches are generally mild and cause little disability.[12,19]

Tension-type headaches are typically bilateral in location; may be described as pressure and may be of a non-pulsating, vice-like quality; tend to be mild or moderate in intensity; and are not aggravated by physical activity.[18] Tension-type headaches are not associated with nausea *and* vomiting; they may be associated with either, but not both.[18]

Patients with Frequent or Daily Headache

Approximately 1% to 2% of adolescents have very frequent headache.[22,23] The old term was "chronic daily headache," but treatments can differ by subtype, so the more precise terms are preferred. The occurrence of both tension and migraine headache can transform over time, with the frequency of attacks increasing over weeks to months until the attacks occur on more days than not.[19]

Specifically, chronic migraine describes the condition in which headaches occur on 15 or more days per month, and the patient may experience the features of migraine headache on at least eight days per month for more than three months.[18] Chronic migraine causes more disability than other chronic headache syndromes, so the majority of youth who seek medical care for frequent headache have chronic migraine.

Medication-overuse headaches should be considered in patients with daily headaches. The diagnosis

Table 1. The SNOOPY Mnemonic

S	**Systemic Disease** History of malignancy or tumor History of congenital heart disease Immunosuppression or immune deficiency Hemotologic — thrombophilia, thrombocytopenia, conagulopathy or sickle-cell disease Genetic disease with predisposition Recent history of head trauma **Signs of Systemic Disease** Constitutional — weight loss, fever, fatigue, malaise, morning vomiting or recurrent vomiting without cause Infectious — sinusitis, encephalitis/meningitis, tickborne Rheumatologic — arthritis, rash
N	**Neurologic Signs** Altered mental status Papilledema Focal neurologic findings New seizure
O	**Onset Sudden** Thunderclap headache — may signal vascular cause
O	**Occipital Location** May be risk factor for secondary headache
P	**Progressive** Chronic or acute progressive pattern **Precipitated by Valsalva** Cough or sneeze triggering a headache may signal increased or decreased intracranial pressure (ICP) **Positional** Worse lying down, awakens patient at night when previously no headache or severe upon wakening may signal ICP Persistently worse with standing may be dehydration, deconditioning, low blood pressure, or low ICP
Y	**Years <6** Risk factor for secondary headache (may be due to limited ability to describe headache)

can occur in patients regularly using one or more medications for acute headache treatment for more than three months; typically, this diagnosis should be considered when patients are using triptans and combination analgesics 10 or more days per month or non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen.[18]

New Daily Persistent Headache

Children and adolescents who do not have a significant history of headache yet begin to experience headaches on a regular or daily basis, and for whom this experience lasts for three months or longer, may have a "new daily persistent headache."[12] New daily persistent headache may be disabling and difficult to treat, but treating as soon as possible after the onset of continuous headache may improve outcomes.[22,24]

Though distinguished by the abrupt onset of symptoms, new daily persistent headache often has features of chronic migraine, and at the initial presentation it may be very similar to an episode of prolonged migraine (status migrainosus).[25] Clinicians may consider the use of bridge therapies — twice-daily naproxen for two weeks or a steroid taper or intravenous medications if the headache is severe or disabling — along with early initiation of preventive migraine therapies including supplements and/or prescriptions.

Trigeminal Autonomic Cephalalgia

This class of headaches — which includes cluster headache, hemicrania continua, paroxysmal hemicrania, and short-lasting unilateral neuralgiform headache attacks — has a very low prevalence in children and adolescents.[26] Some adult patients with cluster headache, however, indicate their headaches began during adolescence.[12]

These headaches are marked by a side-locked headache with unilateral autonomic symptoms on the same side as the pain such as eye tearing, pupillary asymmetry, sweating, and nasal congestion. Constant side-locked headache, even in the absence of cranial autonomic symptoms, can be due to hemicrania continua, which is best treated with indomethacin.[27] Given the unique features and treatments, as well as risk of underlying anatomic causes, any child with a TAC should be referred to Neurology.

Primary Stabbing Headache

These headaches are very brief episodes of stabbing pain without other associated symptoms.[18] The pain is often severe but does not require treatment unless events are frequent.[28] These events typically occur in children and adolescents with other primary headache disorders, such as migraine.[12]

TREATMENT

When patients believe in the effectiveness of their treatment, the treatment is more likely to work. Including the patient in decision-making when developing the treatment strategy may increase the chances of a satisfactory outcome.[29]

The primary care clinician should focus on three major areas when developing a treatment plan for children and adolescents with primary headaches — of which the majority will be migraine — including lifestyle modifications, rescue medications, and preventative agents.

Complementary therapies may be considered as well. Headache specialists may consider other treatment strategies, such as calcitonin gene-related peptide (CGRP) inhibitors or procedures such as nerve blocks and Botox injections, for patients whose symptoms are refractory.

Lifestyle Modifications

Clinicians should counsel patients that lifestyle modifications can be an important part of the treatment plan to decrease headache frequency, regardless of the exact diagnosis.[8] Sleep, hydration and nutrition, activity levels, and behavioral health should all be addressed; if these aspects cannot be optimized, obtaining good headache control may be challenging.[12,19,30-32]

However, patients and their families may have difficulties making changes. Providing practical, realistic advice to families is important; neither patients nor their families should be blamed for the headache syndrome.[33]

All patients with headache should be asked about their sleep pattern in detail.[19,32] Children 3-5 years of age should sleep 10-13 hours per day, children 6-12 years of age should sleep 9-12 hours per day, and adolescents should sleep 8-10 hours per day.[34] Issues with sleep onset may suggest poor sleep hygiene or anxiety. Not staying asleep may suggest sleep apnea or could indicate depression. The importance of good sleep should be reiterated, and barriers to good sleep should be addressed. If improving hygiene is not effective, melatonin can be considered.[13]

Meal irregularity is associated with frequent headaches in children and adolescents.[32] Eating regular meals may reduce the incidence of headaches; fasting can be a migraine trigger. Clinicians should also advise that children older than 9 years of age should consume eight or more cups of water per day.[35]

Sedentary adolescents may have an increased migraine prevalence.[31] Exercise is a beneficial treatment strategy for adults; assessing activity levels and suggesting an active lifestyle in children and adolescents may reduce headaches.[36]

Between 30% and 40% of children and adolescents with migraine have psychiatric comorbidities, with anxiety and depression being the most common.[37-39] Many patients with migraine indicate stress and anxiety are their most common trigger, suggesting treatment for anxiety may be the most important component of migraine treatment. Addressing emotional concerns may help improve headaches in children and adolescents.[40] Cognitive-behavioral therapy has been shown to help improve migraine syndromes in children and adolescents.[41]

Screening for medication overuse is an important part of caring for children and adolescents with headaches. Treatment consists of stopping these medications for a period of about two weeks, followed by reintroduction at an appropriate frequency.[19] Studies in adults suggest starting a daily preventative medication should be considered.[42]

Rescue Medications

All children and adolescents with the diagnosis of migraine should receive a migraine action plan (MAP).[43] The patient's school should be provided with the acute treatment strategy of the MAP, allowing the patient to utilize rescue medications while at school.[12,44]

Practice guidelines recommend ibuprofen 7.5 mg/kg to 10 mg/kg be used three times daily as needed as the first-line treatment for all children and adolescents with headaches.[7] A randomized placebo-controlled trial found ibuprofen to achieve headache relief about 50% of the time, compared to 8% in the placebo group.[44]

If ibuprofen is insufficient, a triptan can be tried in patients diagnosed with migraines.[7] While there are several triptans available, rizatriptan is approved for children 6 years of age and older by the Food and Drug Administration; it is available in a dissolvable tablet, which may be useful in the setting of nausea. Nasal sumatriptan or zolmitriptan, which rely less on enteral absorption, may be helpful for patients who experience severe nausea or vomiting.

Utilizing an antiemetic medication in children and adolescents with headaches and nausea/vomiting should be considered. Metoclopramide, which blocks dopamine, may also help with migraine, but ondansetron can be used as well.[12]

Opioids should not be used for acute or chronic treatment of migraines in children and adolescents.

Preventative Approaches

Preventative treatment should be considered when headaches are frequent and/or life is being disrupted or altered, such as when patients are missing school, activities, or social events. The goals of treatment should be to reduce headache frequency and severity, while also increasing the effectiveness of rescue medications. Shared decision-making between clinicians and families when deciding on a preventative agent is recommended.[8]

Cognitive behavioral therapy for migraine has been shown to reduce headache frequency and migraine disability assessment, regardless of comorbid anxiety and depression, with few adverse events.[45]

Supplements, such as magnesium, riboflavin, and CoQ10, are relatively safe and may be useful for all headache syndromes. Magnesium may help with constipation and anxiety, but should not be used in children with renal insufficiency.[13] Riboflavin may turn the urine bright yellow and should be taken with food to reduce the risk of belly discomfort.[13] CoQ10 may cause upset stomach and difficulty sleeping, so should be given in the morning with food.[13] These agents may be used as a first-line treatment strategy or as an adjunctive strategy for those taking another medication.[19] Scan the QR code on page 67 to access dosing information.

It is important to note that most preventative medication options are no more effective than placebo; studies reveal placebos often improve headache experience compared to no treatment and at rates similar to medications.[8] Nevertheless, clinicians may recommend topiramate, propranolol, and amitriptyline.[8] Cyproheptadine is also often used as a first-line preventative choice, particularly in younger children.[19] When considering a medication for migraine prevention, the clinician should also consider other symptoms and comorbidities, as well as the risks and side effects.

Amitriptyline may help initiate sleep onset, as it may often cause drowsiness. Patients should be informed that amitriptyline may increase the risk of suicide.[8] Some clinicians will obtain an EKG prior to starting amitriptyline.

Propranolol should not be used in patients with asthma or diabetes and may decrease athletic performance. Propranolol may be useful in patients with anxiety but has the potential to worsen depression.

Topiramate can reduce appetite and may be useful in patients with a high BMI interested in decreasing their weight. However, mental fogginess and word-finding difficulties may develop, and topiramate should be avoided in patients with glaucoma or kidney stones. Clinicians must counsel that topiramate can have teratogenic effects and prescribe daily folic acid supplementation to patients of childbearing potential who take topiramate.[8]

Cyproheptadine can cause drowsiness and may be useful in patients with sleep onset difficulties. It can also stimulate the appetite and might be useful in patients who are underweight.

Finally, patients with an aura should avoid oral contraceptives that contain estrogen.

CONCLUSION

The primary care clinician can help many patients with headache by performing a thoughtful and directed evaluation, and initiating some basic, but very important treatment strategies. The sample case on the next page is offered as a reference for readers.

SAMPLE CASE

History and Exam

A 12-year-old male presents with a chief complaint of headache that started about eight months ago, a few months after his last well-child visit when he was doing well, with no concerns. Headaches seem to occur a few times per week but are not getting worse. They usually occur in the afternoon and can last for two to four hours. The headaches occur in the frontal region of his head and often on the left side. The discomfort is throbbing in nature and generally associated with light and noise sensitivity. With the more severe headache, he often describes nausea. The headaches seem to occur more often when he has not had a good night sleep the night before.

Headaches do not wake him from sleep, and he does not wake up in the morning with headaches. He also denies any neurological concerns such as weakness or issues with his balance. Ibuprofen and lying down in a dark quiet room help, and if he falls asleep, the headache is usually gone when he wakes up. He has not missed any full days of school but has needed to leave school early a few times and has missed a few basketball practices because of a headache. When he does not have a headache, he feels well and has no other medical concerns.

He has no significant past medical history. His parents divorced about four years ago, and he had received some counseling during that time. There is a family history of migraines. His general and neurological exams, including fundoscopic evaluation, are normal.

Assessment

Based on history and exam, concern for a secondary headache is low. The diagnosis of migraine without aura is made.

Plan

1. Lifestyle Modifications
    a. Sleep appears to be a trigger, and on further questioning, this might improve with attention to his sleep hygiene, specifically when he is at his father's house.
    b. This patient's anxiety can be a trigger, and therapy is recommended.
    c. Education is added regarding the need for regular meals and drinking plenty of fluids.
2. Rescue Medications
    a. Rizatriptan is added to the ibuprofen for use when headaches develop.
    b. Documentation regarding his migraine action plan is provided so he can take the rescue medications while at school as soon as the headache starts.
3. Prevention
    a. Headache prevention strategies are discussed. For now, he may consider using over-the-counter magnesium 200 mg and riboflavin 200 mg nightly. If initial strategies don't suffice, prevention medications may be prescribed.

Follow-Up

He returns for follow-up in a few months and indicates the headaches are improved. They are less frequent and less severe when he gets them. He is doing much better with his sleep at his father's house. He has an initial appointment for counseling in the next few weeks. The rizatriptan appears to be working well and resolves the headache in about 20 minutes. He is taking magnesium and riboflavin most days and feels this is helping. He has not missed any school or activities since the last appointment.

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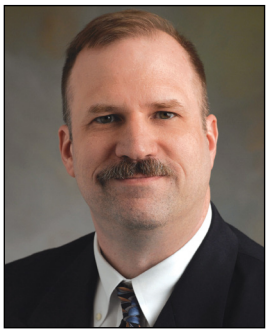
A Case-Based Approach to Thrombocytopenia in Adults

Part 2: Additional Cases and Conclusion

Brennan



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Thrombocytopenia is a vast topic with a differential ranging from lab artifacts like pseudothrombocytopenia to immediately life-threatening events such as microangiopathic hemolytic anemia. This case-based discussion demonstrates key aspects of common and uncommon causes of thrombocytopenia in adults. Etiologies may be delineated as the result of decreased production or increased consumption.

In the first part of this series published last year, we reviewed the differential diagnosis and an approach to thrombocytopenia using four cases (numbered 1-4) to illustrate key points.[1] In this second part, we conclude with four additional cases (numbered 5-8) that exemplify the broad differential and nuances of approaching thrombocytopenia in the adult.

CASE 5: A 37-year-old male with a history of cryptogenic strokes and chronic kidney disease (CKD) with a baseline creatinine of 1.4 mg/dL presents to the Emergency Department with bright red blood per rectum. He is already on chronic anticoagulation with warfarin. Labs done at the time of presentation demonstrate severe thrombocytopenia with a normal hemoglobin.

WBC Count (4.8-10.8 10*3/µL)	7.2
Hgb (14.0-18.0 g/dL)	14.8
MCV (80.0-100.0 fL)	88.2
Platelet Count (150-450 10*3/µL)	4▼
Neutrophils Absolute (2.20-8.00 10*3/µL)	5.04
Creatinine (0.7-1.2 mg/dL)	1.4▲
Protein Total Serum (5.6-7.9 g/dL)	6.2
Albumin (3.5-4.9 g/dL)	4.3
Bilirubin Total (0.2-1.2 mg/dL)	2.4▲
Alkaline Phosphatase (34-104 U/L)	56
AST (SGOT) (13-40 U/L)	34
ALT (SGPT) (7-52 U/L)	44
INR (PT) (0.9-1.2)	3.0▲
PTT (23.9-30.7 s)	45.5▲

Prothrombin time (PT) and partial thromboplastin time (PTT) are prolonged consistent with the use of the vitamin K antagonist. The presumed diagnosis is immune thrombocytopenic purpura, for which intravenous immunoglobulin (IVIG) and pulse dexamethasone are initiated; this results in a transient increase in platelet count to 15,000/µL, which then quickly returns to less than 10,000/µL.

The patient then develops stroke-like symptoms, and the differential is broadened to include thrombotic thrombocytopenic purpura (TTP). The diagnostic test of choice, an ADAMTS13 level, may take three days or more, so a PLASMIC score is calculated and indicates a high pretest probability prompting therapeutic plasma exchange (TPE) to treat for TTP. Furthermore, a peripheral smear shows an increase in schistocytes and microspherocytes and a mean corpuscular volume (MCV) of <90 fL. This case illustrates that a normal hemoglobin does not eliminate the possibility of a microangiopathic process, and because the total bilirubin is elevated, further workup is initiated.

His lactate dehydrogenase (LDH) is found to be extremely high at 1,517 U/L (normal <260 U/L), while the haptoglobin is undetectable; later it is noted that these labs had been drawn after IVIG was given. IVIG can result in a hemolytic anemia, so it is important to check these hemolytic values prior to initiating IVIG, if at all possible.

The ADAMTS13 level subsequently demonstrates very low activity consistent with the diagnosis of TTP:

Result Name	Value	Unit	Reference Value
▼ LOW **ADAMTS13 Activity Assay**	9	%	≥70
▲ HIGH **ADAMTS13 Inhibitor Bethesda Titer**	1.5	Bethesda units	≤0.4

Plasma exchange results in the rapid resolution of thrombocytopenia; following this, the patient receives rituximab, which returns the ADAMTS13 to a normal level. Given the prior stroke-like symptoms, his ADAMTS13 level is monitored periodically, and the patient receives rituximab every one to two years

when levels are dropping. Fortunately, he has not had a stroke in the more than five years since he first presented with TTP.

Discussion

The PLASMIC score is much like the 4T score for heparin-induced thrombocytopenia in that it gives a pretest probability of TTP — one point each is assigned for the following: platelet count <30,000/µL, hemolysis, no active cancer, no solid organ or stem cell transplant, MCV <90 fL, international normalized ratio (INR) <1.5, creatinine <2 mg/dL. Those with a low score are unlikely to have TTP, but those with intermediate or high scores should have their ADAMTS13 levels tested and should receive therapy for TTP until another diagnostic conclusion is reached.[2]

ADAMTS13 is a protease that cleaves ultra-large von Willebrand multimers. Without this activity, von Willebrand multimers continue to activate platelets, resulting in a microangiopathic process. TTP can be hereditary due to deficiencies in ADAMTS13 itself, or TTP can be immune mediated, such as in the case described here, in which an acquired inhibitor against the ADAMTS13 molecule prevents its function. Critical illness can result in lower-than-normal levels. Yet in true TTP, levels are often critically low (<10%). Asking Hematology services to help interpret findings may be beneficial when the ADAMTS13 activity level is >10%.[3]

Immune TTP has an incidence of 3 in 1,000,000 individuals, and the clinical presentation is often multisystemic. Common symptoms include nausea and abdominal pain, bleeding and purpura, weakness, neurologic findings — including headache, confusion, stroke, or seizure — and cardiac ischemia.[4,5] Mild renal insufficiency is common, but more severe renal injury should raise the concern for an alternative microangiopathic process such as Shiga toxin-induced hemolyticuremic syndrome (HUS), complement-mediated HUS, or drug-induced thrombotic microangiopathy. These symptoms may not be seen early in the course; severe thrombocytopenia should always result in a consideration of the diagnosis of TTP.

Treatment involves a high clinical suspicion and may need to be initiated prior to results of confirmatory testing with ADAMTS13 since untreated TTP has a mortality rate as high as 90%. TPE removes ultra-large von Willebrand multimers, in place of which the patient is given donor plasma that contains normal von Willebrand multimers. At the same time, corticosteroids suppress the immune system. When TPE is completed, rituximab is initiated to further suppress the immune-initiated pathophysiology.

Caplacizumab is a monoclonal antibody that blocks the activity of von Willebrand interactions with platelets and is used in severe or relapsing cases.[6] Finally, if there is serious bleeding or the need for an invasive procedure, platelet transfusion appears to be safe and effective.[7]

Diagnosis: thrombotic thrombocytopenic purpura

- Consider hemolysis labs (LDH and haptoglobin) in severe thrombocytopenia.
  - Check prior to IVIG.
- PLASMIC scores help evaluate the pretest probability of TTP.
  - Intermediate or high-risk scores can be assessed with an ADAMTS13 and should lead to presumptive treatment with plasma exchange.
- Check HBcAb prior to IVIG.

CASE 6: An 86-year-old female who lives alone presents to the Emergency Department with several weeks of right leg pain and swelling due to a deep vein thrombosis. Her son notes she has unintentionally lost 20 pounds over the past few months and is becoming increasingly forgetful.

A computed tomography (CT) scan of the chest, abdomen, and pelvis shows no malignancy. Pancytopenia noted with a macrocytic anemia and elevated total bilirubin raises the possibility of a hemolytic process; that is confirmed when lab results further show a very high LDH (1,836 U/L, normal <260 U/L) and undetectable haptoglobin. A direct antiglobulin test is negative, and coagulation studies are unremarkable.

WBC Count (4.8-10.8 10*3/µL)	2.4▼
Hgb (12.0-16.0 g/dL)	8.1▼
MCV (80.0-100.0 fL)	105.4▲
Platelet Count (150-450 10*3/µL)	123▼
Neutrophils Absolute (2.20-8.00 10*3/µL)	1.39▼
Lymphocytes Absolute (0.90-5.00 10*3/µL)	0.93
Monocytes Absolute (0.20-0.80 10*3/µL)	0.05▼
Eosinophils Absolute (0.00-0.40 10*3/µL)	0.03
Basophils Absolute (0.00-0.40 10*3/µL)	00.0
Creatinine (0.6-1.1 mg/dL)	0.6
Protein Total Serum (5.6-7.7 g/dL)	5.7
Albumin (3.5-4.9 g/dL)	3.4▼
Bilirubin Total (0.2-1.1 mg/dL)	1.8▲
Alkaline Phosphatase (34-144 U/L)	62
AST (SGOT) (13-40 U/L)	40
ALT (SGPT) (7-52 U/L)	17

When subsequently checked, the patient's B_{12} level is undetectable. Treatment with B_{12} supplementation results in resolution of the patient's cytopenia and improvement in fatigue and memory.

Discussion

In this age group, a pancytopenia with macrocytic anemia and weight loss is often a sign of an underlying hematologic malignancy such as myelodysplastic

syndrome (MDS) or a metastatic carcinoma. Yet, severe B12 deficiency can also result in ineffective erythropoiesis and intramedullary hemolysis.

B12 deficiency is often caused by a loss of intrinsic factor due to autoimmune atrophic gastritis, also known as pernicious anemia. Other causes include a chronic deficiency, such as can occur when maintaining a vegan diet or in the setting of a patient with a history of gastric bypass, short gut syndrome, inflammatory bowel disease, Imerslund-Gräsbeck syndrome, or chronic use of metformin. Prolonged use of nitrous oxide, as may be seen in patients who use this drug recreationally, may further result in a functional B12 deficiency.

Clinical features are megaloblastic anemia with a hypercellular and dysplastic bone marrow that can look like MDS or leukemia, as well as demyelination of the cervical and thoracic dorsal and lateral columns of the spinal cord and white matter of the brain. Subacute combined degeneration can result in symmetric paresthesia, impaired position and vibration sensation, gait disorders, or memory issues.[8]

Testing the serum B12 levels is subject to spuriously reduced and elevated levels due to fluctuations in binding proteins. Therefore, interpreting the value in the clinical context is essential. For example, pregnancy can be a time of falsely low levels, and malignancy can result in falsely elevated levels.

Furthermore, anti-intrinsic factor antibodies in pernicious anemia can compete with the chemiluminescence assay and result in a spuriously normal level. Checking methylmalonic acid (MMA) levels can aid in the diagnosis of B12 deficiency as MMA is high in B12 deficiency. Providers must remember, however, that MMA can be falsely elevated in the setting of renal insufficiency.[7]

Treatment involves intramuscular or subcutaneous injection of B12 in severe/symptomatic cases to quickly raise the B12 level. Oral supplementation with 1,000 mcg daily of cyanocobalamin is typically sufficient to overcome absorption issues thereafter. When there is clinical uncertainty of B12 deficiency, replacement is indicated since missing the diagnosis may result in significant long-term consequences.

DIAGNOSIS: severe B12 deficiency with associated ineffective erythropoiesis and intramedullary hemolysis

- Check B12 during the workup of thrombocytopenia and consider checking MMA or empirically treating with B12 to gauge the symptom response.

CASE 7: A 79-year-old male with a history of severe aortic stenosis presents with one week of nausea/vomiting that initially improved until he developed a fever to 102°F and confusion. Vital signs include a blood pressure of 108/72 with pulse of 90 beats per minute. A CT of the chest, abdomen, and pelvis without intravenous or oral contrast demonstrates bibasilar atelectasis versus pneumonia, borderline hepatomegaly, and possible right perinephric stranding. Labs performed during admission show severe thrombocytopenia with neutrophilia, acute kidney injury, hyponatremia, and transaminitis.

WBC Count (4.8-10.8 10*3/µL)	17.0▲
Hgb (14.0-18.0 g/dL)	13.9▼
MCV (80.0-100.0 fL)	93.5
Platelet Count (150-450 10*3/µL)	48▼
Neutrophils Absolute (2.20-8.00 10*3/µL)	12.84▲
Lymphocytes Absolute (0.90-5.00 10*3/µL)	3.83
Monocytes Absolute (0.20-0.80 10*3/µL)	0.29
Glucose (serum) (65-140 mg/dL)	118
Sodium (135-145 mmol/L)	130▼
Potassium (3.4-5.3 mmol/L)	3.7
Chloride (98-107 mmol/L)	87▼
CO2 Venous (21.0-31.0 mmol/L)	31.0
Anion Gap (5-15 mmol/L)	12
Creatinine (0.80-1.30 mg/dL)	3.92▲
BUN/Creatinine Ratio (10-20 Ratio)	19
Protein Total Serum (5.6-7.7 g/dL)	6.1
Albumin (3.5-4.9 g/dL)	3.5
Bilirubin Total (0.2-1.2 mg/dL)	1.5▲
Alkaline Phosphatase (34-104 U/L)	328▲
AST (SGOT) (13-40 U/L)	117▲
ALT (SGPT) (7-52 U/L)	104▲

In the Emergency Department, he is given ceftriaxone and azithromycin and soon switched to piperacillin/tazobactam and vancomycin for presumed sepsis. Blood and urine cultures are subsequently negative, and a viral panel including COVID-19 testing is negative as well; urine legionella and pneumococcal antigens are negative.

Given that the patient has mental status changes, an elevated total bilirubin, and thrombocytopenia in the setting of acute kidney injury requiring dialysis, the differential diagnosis includes the possibility of a microangiopathic hemolytic anemia. Further lab analysis reveals that LDH is elevated to 563 U/L (normal <260 U/L) and the haptoglobin and reticulocyte counts are normal. PT/PTT are also normal, and the fibrinogen is appropriately elevated.

Broad-spectrum antibiotics do not seem to help the fever. In the setting of borderline hepatomegaly, hemophagocytic lymphohistiocytosis is also considered. His ferritin is elevated to 6,222 ng/ml (normal <336 ng/ml), and the triglycerides are also elevated at 216 mg/dL (normal <150 mg/dL). Soluble IL2r alpha (CD25) is sent, and although it does not result until days after a diagnosis is ultimately made, it is highly elevated at 28,950 pg/ml (upper limit of normal 1,891 pg/ml).

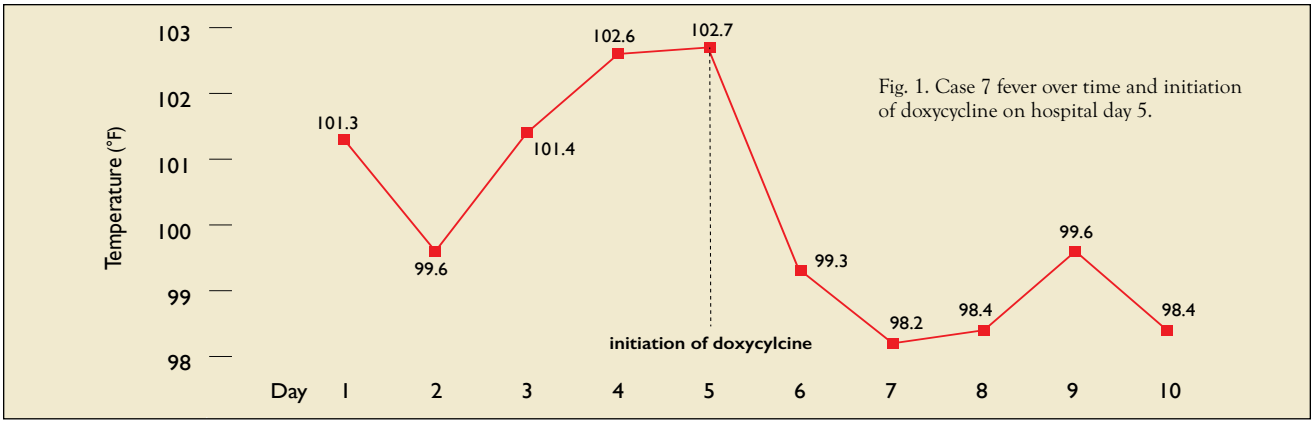

Fig. 1. Case 7 fever over time and initiation of doxycycline on hospital day 5.

Specialists from the Infectious Diseases and Hematology services are consulted, and a tickborne illness is also considered in the differential; empiric doxycycline is started on hospital day five. Immediate defervescence is noted. Lab analysis demonstrates that the platelet count starts recovering 48 hours later and is back to normal range within five days (see Fig. 1 above).

Additional lab results are revealed several days after the diagnosis of human granulocytic anaplasmosis is made — including *Ehrlichia* human granulocytic ehrlichiosis immunoglobulin M (IgM) antibody at a ratio of 1:80 and IgG antibody at a ratio of 1:64. The following lab results are negative: *Ehrlichia* IgM and IgE, *Rickettsia rickettsii* panel, Lyme titers, and Babesia titers. Q fever IgM stages I and II are negative, while IgG stages I and II are positive, suggesting either a past exposure or a false positive. Epstein-Barr virus titers suggest a prior infection. On further review of the history when his sensorium improves, the patient relates that he had gone camping in the woods one week prior to the onset of these symptoms, although he does not recall any tick bites.

Discussion

Human granulocytic anaplasmosis is caused by *Anaplasma phagocytophylum* and has an incubation of one to two weeks. It is more commonly seen in the northeastern United States.[9,10] The diagnosis can be made if Wright- or Giemsa-stained peripheral blood during the early stage of infection demonstrates the obligate intracellular parasite, or morulae, in the cytoplasm of neutrophils. Fig. 2 (at right above) demonstrates a case of *Ehrlichia*.

Acute and convalescent serologic testing may demonstrate a four-fold change or seroconversion; this is the most sensitive and most widely used test. Treatment decisions typically need to be made prior to knowing the results of testing; the serology can be negative in the first one to two weeks of infection. Polymerase chain reaction amplification for specific DNA may be positive in the first week of infection but is not widely available.

In symptomatic patients, doxycycline is the treatment of choice. Empiric therapy with doxycycline is justified when considering this diagnosis because it will cover other tickborne illnesses — with the exclusion of *Babesia* — which occur in 2% to 12% of cases.[10,11] Quick resolution of fever after starting doxycycline can be "diagnostic" of tickborne illness, and if symptoms are not improving within 48 hours, an alternative diagnosis should be considered.

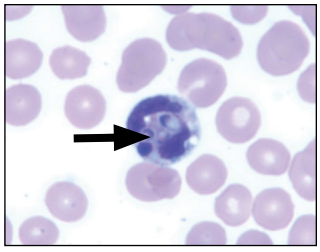

Fig. 2. Case 7 morulae at 1000x. This peripheral smear demonstrates the intracytoplasmic morulae within a monocyte from a case of *Ehrlichia*. Note that *Anaplasma* as described in this case infects the neutrophil lineage.

Image courtesy Angie Ha, LG Health Core Lab supervisor.

The constellation of non-specific flu-like symptoms including fever, muscle aches, and nausea, along with transaminitis, acute kidney injury, and hematologic derangements including leukopenia, atypical lymphocytosis, bandemia, and thrombocytopenia as described in this case, should prompt the care team to consider tickborne illness among many other life-threatening etiologies. The non-specific presentation makes it tempting to assume thrombocytopenia is consumptive, such as might occur in a patient who is septic. The presentation is variable from asymptomatic to life threatening in 3% of cases.[10]

DIAGNOSIS: tickborne Illness — human granulocytic anaplasmosis

- Include a history of outdoor activity in the evaluation of thrombocytopenia during tick exposure months.
- Rapid resolution of symptoms and thrombocyto-

penia with doxycycline can be diagnostic of a tickborne illness.

CASE 8: A 62-year-old male presents to the Hematology clinic prior to having a right total knee arthroplasty. He has a long-standing history of platelets in the 60,000-90,000/µL range. He explains that when his father had a myocardial infarction, it was noted that the father's platelets were in the 70,000-80,000/µL range; subsequently, the patient's brother was noted to have platelets in the 40,000/µL range.

The patient states that when he was a child, he was told he has an autosomal dominant trait most consistent with hereditary macrothrombocytopenia. He has had multiple hemostatic challenges in the past without excessive bleeding including a circumcision, a dental extraction, several broken bones including a C5 fracture, an ACL repair, and a vasectomy.

Von Willebrand testing is normal, and platelet aggregation studies are overall unremarkable. A peripheral smear shows enlarged platelets with an absolute thrombocytopenia (see Fig. 3).

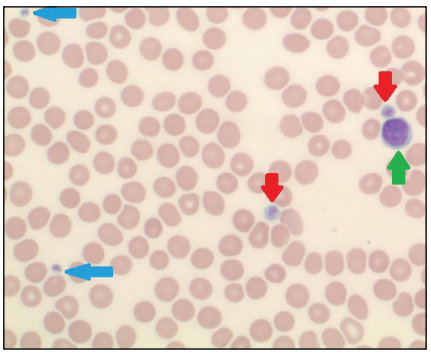

Fig. 3. Case 8 peripheral smear at 60x shows macrothrombocyte (red arrows) and more normal size platelets (blue arrows), as well as a lymphocyte (green arrow) in a background of red blood cells.

He proceeds with knee surgery without any bleeding complications and tolerates prophylactic aspirin.

Discussion

Hereditary macrothrombocytopenia can be found in patients of a variety of genetic heritages and is characterized by large to giant platelets with an absolute thrombocytopenia that is either clinically insignificant or results in a mild bleeding disorder.[12] Heterozygous mutations in GP1BA or GP1BB likely account for this condition, and there is overlap genetically with patients who have Bernard-Soulier syndrome.[13]

DIAGNOSIS: congenital thrombocytopenia most consistent with hereditary macrothrombocytopenia

- A long-standing history of stable thrombocytopenia in a young person should prompt consideration of a congenital etiology.

CONCLUSION

As these cases demonstrate, the differential diagnosis for thrombocytopenia can be broad and complex. Understanding the differential as presented in these two articles will allow a clinician to consider life-threatening etiologies and initiate the appropriate workup. Astute clinicians should keep in mind the need to have a high index of suspicion for heparin exposure, microangiopathic hemolytic processes, and tickborne illness.

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Pharmacologic Considerations for MASLD and MASH

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In 2023, metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) replaced the former nomenclature of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH). The purpose of the update was to remove exclusionary and stigmatizing language of the previous terminology. Additionally, a new diagnosis (MetALD) helps to recognize patients who have features of MASLD along with increased alcohol intake.

MASLD is the most common chronic liver disease around the world, likely impacting more than 30% of the global population. By the year 2040, the prevalence rate of MASLD in adults is expected to increase to over 55%. Despite the growing prevalence, less than 5% of patients with MASLD are aware of their liver disease. A more aggressive form of MASLD is MASH, which is the leading cause of liver cancer and number one cause for liver transplantation among women.[1-3]

Current guidelines for the diagnosis and management of MASLD and MASH include the 2023 American Association for the Study of Liver Diseases (AASLD) Practice Guidance on the clinical assessment and management of nonalcoholic fatty liver disease and the 2024 EASL/EASD/EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease.[4,5] Additionally, guidelines were recently published to address the FDA approval of resmetirom.[6]

Diagnosing MASLD may mean recognizing several aspects of the history and physical exam, including the presence of steatotic liver disease identified by imaging or biopsy, at least one cardiometabolic criteria defined in the guidelines, and no other identified causes of steatosis. The diagnosis of MetALD incorporates the same three diagnostic criteria as MASLD in addition to alcohol intake of ≥20 grams per day (females) or ≥30 grams per day (males).[5] Of note, a standard drink – 12 ounces of regular beer, 5 ounces of wine, 1.5 ounces of distilled spirits – typically contains 14 grams of alcohol. On average, 20% of patients with MASLD progress to MASH, which is hepatic steatosis with inflammation and hepatocyte ballooning on imaging. Progression of disease is relatively slow; however, progression may be faster in patients with cardiometabolic risk factors of type 2 diabetes mellitus (T2DM) and obesity.[1]

In primary care settings, patients suspected to have MASLD based on metabolic risk factors or imaging should undergo primary risk assessment. The fibrosis-4 (FIB-4) index is a non-invasive tool used to identify patients who may advance to fibrosis and is calculated using a patient's age in years, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in units/L, and platelet count in 10^9/L. The score is calculated as:

$$\text{FIB-4} = \frac{(\text{age} \times \text{AST})}{\text{platelet count} \times \sqrt{\text{ALT}}}$$

The FIB-4 score should be used to screen patients with T2DM, obesity, and ≥1 cardiometabolic risk factor, or persistently elevated liver enzymes. If the FIB-4 score is <1.3, then the score should be reassessed every one to three years based on T2DM diagnosis and number of metabolic risk factors, and every one to two years for patients with T2DM or pre-T2DM or if they have ≥2 metabolic risk factors.

Previous terminology referenced throughout the article matches terminology utilized in clinical trials prior to updated nomenclature.

The FIB-4 score can be reassessed every two to three years if the patient does not have T2DM or has <2 metabolic risk factors. If the FIB-4 score is between 1.3 and 2.67, intensified management of comorbidities is warranted including lifestyle interventions, treatment of comorbidities, or bariatric procedures. For scores >2.67, a referral to a hepatologist is recommended. See Table 1 for a summary of management recommendations. All patients with clinical suspicion of MASLD should have ongoing assessment of alcohol intake, lifestyle management, and cardiometabolic risk reduction and preferential use of medications with potential MASLD benefit.[4,5]

The management of MASLD is multi-faceted and incorporates both non-pharmacologic and pharmacologic interventions. For those with overweight/obesity, weight loss of 3% to 5% has been shown to improve steatosis; however, weight loss of >10% is generally required to improve MASH and fibrosis.

The Mediterranean diet has been associated with cardiovascular health and reduction in liver fat. If unable to follow the Mediterranean diet, a diet leading to a caloric deficit with limited carbohydrates and saturated fat, and enriched with high fiber and unsaturated fats, should be recommended. Studies have shown regular moderate exercise at least five times per week for a total of 150 minutes per week or an increase in activity level by more than 60 minutes per week can prevent or improve MASLD. Exercise should be routinely recommended and individualized to the patient's physical abilities.[4-7]

Several medications may improve parameters of MASLD; however, the only FDA-approved agent currently on the market for the treatment of MASLD or MASH is resmetirom. Non-FDA-approved agents that may have some benefit in MASLD or MASH include pioglitazone, vitamin E, injectable semaglutide, and tirzepatide (see Table 2 on page 82).

Resmetirom is a partial agonist of thyroid hormone receptor-beta (THR-β), which is the predominant thyroid hormone receptor in the liver. The stimulation of THR-β in the liver reduces intrahepatic triglycerides. Resmetirom is FDA approved for noncirrhotic MASH with moderate to advanced fibrosis (F2-F3). If the patient's actual body weight is less than 100 kg, then 80 mg by mouth once daily is recommended. If the patient's actual body weight is 100 kg or more, the recommended dose is 100 mg once daily.[8] If patients are utilizing a concomitant moderate cytochrome P450 2C8 inhibitor (e.g., clopidogrel), the recommended dosage is 80 mg daily for those 100 kg or more or 60 mg daily for those who weigh less than 100 kg.[6]

Resmetirom therapy is recommended in patients with liver histology showing MASH with stage 2 to 3 liver fibrosis or stipulated on their imaging-based non-invasive liver disease assessment. If a biopsy is not available, the preference is to use a liver stiffness test measuring vibration-controlled transient elastography and/or magnetic resonance elastography, based on the MAESTRO-NASH trial and AASLD guidelines. Resmetirom is not recommended in patients with concomitant active liver disease, excess alcohol use, active thyroid disease, or cirrhosis. Patients with other liver stiffness measurements could be considered by a specialist experienced in liver fibrosis for the initiation of resmetirom therapy.[4,6,9,10]

Routine monitoring for safety and efficacy is recommended for patients on resmetirom. Before treatment initiation, a hepatic function panel, thyroid function tests, lipid panel, and a non-invasive measurement of liver stiffness is recommended. After three months of treatment, a hepatic function panel should be obtained. After six months of treatment, a hepatic function panel, thyroid function panel, and lipid panel are recommended, and at 12 months an assessment of response. If there is worsening of non-invasive liver disease assessment or a consistent increase in ALT, resmetirom therapy should be stopped.

Resmetirom therapy may be continued if a beneficial response is shown after 12 months of therapy. A beneficial response to resmetirom therapy is defined as either an improvement in liver stiffness measure or the normalization or significant improvement in ALT (defined as a decrease in ALT by 17 units or a 20% decline). Improvement in liver stiffness measure is defined as an improvement in vibration-controlled transient elastography by ≥25% or magnetic resonance elastography by ≥20% from baseline.[6,10]

Statin therapy can be utilized while patients are on resmetirom therapy but may need to be modified. While taking resmetirom, it is recommended not to exceed a daily dose of 40 mg of atorvastatin or pravastatin, and 20 mg of rosuvastatin and simvastatin.[6]

In the MAESTRO-NAFLD-1 trial, resmetirom 80 mg and 100 mg were compared to placebo over the course of 52 weeks in patients with NAFLD and presumed NASH. The primary endpoint of the study was the incidence of treatment-emergent adverse events

Table 1. **FIB-4 Risk Stratification and Referral to GI**[3]

FIB-4 Score	Presence of Cardiometabolic Comorbidities*	Management	Reassessment Interval
<1.3	No presence of diabetes *and* <2 metabolic risk factors	Manage by PCP	Every 2-3 years
<1.3	T2DM *or* ≥2 metabolic risk factors	Manage by PCP	Every 2-3 years
1.3 - 2.67	Any	Consider referral to GI/liver specialist	n/a
>2.67	Any	Refer to GI/liver specialist	n/a

** Cardiometabolic criteria*

1. *Body mass index ≥25 kg/m² (≥23 for Asian patients)* ***or*** *waist circumference >94 cm (male) or >80 cm (female) or ethnicity adjusted.*
2. *Fasting serum glucose ≥100 mg/dL* ***or*** *two-hour post-load glucose levels ≥140 mg/dL* ***or*** *HbA1c ≥5.7%* ***or*** *type 2 diabetes* ***or*** *treatment for type 2 diabetes.*
3. *Blood pressure ≥130/85* ***or*** *specific antihypertensive drug treatment.*
4. *Plasma triglycerides ≥150 mg/dL* ***or*** *lipid-lowering treatment.*
5. *Plasma HDL cholesterol ≤40 mg/dL (male) and ≤50 mg/dL (female)* ***or*** *lipid-lowering treatment.*

over 52 weeks. Secondary endpoints included LDL-C, apoB, triglycerides, hepatic fat, and liver stiffness. The study found resmetirom was well tolerated among the participants. Resmetirom was also found to improve markers of liver injury and reduce the levels of LDL-C, apoB, and triglycerides.[11]

In the phase 3 MAESTRO-NASH trial, resmetirom 80 mg and 100 mg were compared to placebo over the course of 52 weeks in patients with biopsy-confirmed NASH and a fibrosis stage of F1B, F2, or F3. The two primary endpoints were NASH resolution with no worsening of fibrosis and an improvement in fibrosis by at least one stage with no worsening of the NAFLD activity score. The study found 25.9% of participants in the 80 mg group, 29.9% of participants in the 100 mg group, and 9.9% of participants in the placebo group demonstrated NASH resolution with no worsening of fibrosis.

Fibrosis improvement by at least one stage with no worsening of the NAFLD activity score was achieved in 24.2% of participants in the 80 mg group, 25.9% in the 100 mg group, and 14.2% of participants in the placebo group. Both primary endpoints were found to be statistically significant, and resmetirom was found to be superior to placebo. The study concluded both doses of resmetirom were superior to placebo with respect to resolution of NASH and improvement in liver fibrosis by at least one stage.[9]

Pioglitazone is a thiazolidinedione that acts as a peroxisome proliferator-activated receptor (PPAR)-γ activator. It improves insulin sensitivity and causes lipid metabolism within the adipose tissue, liver, and muscles. Historically, it is indicated for the management of T2DM.[12] In a 2006 study, pioglitazone was compared to placebo in patients with biopsy-confirmed NASH over a six-month period. The study found pioglitazone provided improvement in liver histology for those with NASH and T2DM. Conversely, the study found a significant increase in weight gain with pioglitazone therapy as compared to placebo.[13]

Vitamin E is an antioxidant that has been shown to reduce hepatocellular injury due to oxidative stress. A 2019 study completed with patients within the U.S. Department of Veterans Affairs compared vitamin E 400 units orally twice daily with or without pioglitazone 45 mg daily to placebo over the course of 18 months. The study found the combination of vitamin E and pioglitazone provided significant benefit regarding the improvement of liver histology for patients with NASH and T2DM. The study authors suggest that monotherapy of vitamin E should not be recommended for patients with NASH because it does not improve liver histology compared to placebo.[14]

In patients with biopsy-confirmed NASH without T2DM, a 2010 study compared the use of pioglitazone, vitamin E, or placebo over the course of 96

Table 2. Review of Current Literature on the Pharmacologic Management of MASLD/MASH		
Agents	**MASH Benefits with T2DM**	**MASH Benefits without T2DM**
Resmetirom	X (FDA approved)	X
Pioglitazone	X	X
Vitamin E		X
Injectable Semaglutide	X	X
Tirzepatide	X	X

weeks. Participants received pioglitazone 30 mg daily, vitamin E 800 units daily, or placebo. In comparison to placebo, vitamin E was superior for the treatment of NASH in adults without T2DM. The study authors found pioglitazone did not provide significant improvement in histologic features of NASH, but it did provide a significant improvement in inflammation and steatosis.[15]

Semaglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist. Mechanistically, GLP-1 receptor agonists act within the incretin pathway to decrease appetite, insulin resistance, and liver fat, which are all advantageous in MASLD and MASH. Semaglutide currently has FDA-approved indications in T2DM and weight management.[16] In a phase 2 trial, injectable semaglutide was compared to placebo in patients with biopsy-confirmed NASH and fibrosis, with or without T2DM, and a BMI of greater than 25 kg/m^2. Participants were randomized to receive either a 0.1 mg, 0.2 mg, or 0.4 mg subcutaneous daily dose of semaglutide, or a placebo. The 72-week-long trial found a significant resolution of NASH in patients with or without T2DM as compared to placebo. There was no significant improvement in fibrosis in the semaglutide group as compared to placebo. The use of semaglutide was found to cause a weight loss of 13% from baseline, while placebo led to only 1% weight loss.[17]

Tirzepatide is a novel agent that is a GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) dual receptor agonist.[18] The phase 2 SYNERGY-NASH trial compared tirzepatide to placebo in patients with biopsy-confirmed NASH and stage F2 or F3 (moderate or severe) fibrosis. Participants received either 5 mg, 10 mg, or 15 mg once weekly of tirzepatide as compared to placebo for 52 weeks. The study found tirzepatide was more effective in resolution of NASH without worsening of fibrosis as compared to placebo after 52 weeks.[19]

The use of sodium glucose cotransporter 2 (SGLT-2) inhibitors as a MASH-targeted therapy in patients with MASH is not recommended. There is currently insufficient evidence to support utilizing SGLT-2 inhibitors for MASH. For patients with MASLD, SGLT-2 inhibitors are safe to use and are recommended to be used for the appropriate comorbid conditions of T2DM, heart failure, or chronic kidney disease.[6]

The pipeline of medications for the management of MASLD and MASH is promising with new clinical targets. Approaches under investigation include hepatic lipid accumulation and the resultant metabolic stress. Agents to target this include PPAR agonists (lanifibranor, saroglitazar); another approach focuses on targeting fibrosis, oxidative stress, and inflammation. These agents include tumor necrosis α pathway regulators (emricasan, ZSP1601) and immune modulators (cenicriviroc, belapectin). An additional approach for MASLD management targets the gut. These agents include solithromycin and IMM-124e.[20]

As the prevalence of MASLD and MASH continues to increase, the detection and early screening of these are crucial to control contributing comorbid conditions and prevent progression to fibrosis or cirrhosis. Routine risk reassessment, lifestyle interventions, and intensive management of metabolic comorbid conditions may prevent further complications.

The pharmacologic management of MASLD and MASH is evolving. There is currently only one FDA-approved agent for the management of MASH, but several agents have been shown to improve disease markers for patients. Agents focusing on new clinical targets suggest a promising future in the management of MASLD and MASH.

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PHOTO QUIZ FROM APP PROGRAM ONBOARDING

A Handful of Trouble

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CASE HISTORY

A 66-year-old female presents to the office with complaints of a sore on her left dorsal hand that initially presented 10 days ago. She first noticed the sore after scraping her hand against a car seat resulting in mild swelling and erythema; she did not experience skin breakdown (see Fig. 1). The patient reports it feels like a foreign object is in her hand.

She has already tried lancing it herself at home, after which a small amount of old blood was released, but it remains painful. The left hand has what appears to be an abscess that is mobile, soft, round, and erythematous, measuring approximately 1 x 1 cm in size; it is not warm to the touch.

The patient denies any fevers, myalgias, or chills. Concurrently, she began Keflex® for group A streptococcal pharyngitis two days prior to presenting to the office. She further relays that she actively swims in a chlorinated pool two days a week and takes Plaquenil® and methotrexate for rheumatoid arthritis. It is recommended that she continue Keflex® and topical Bactroban™ for suspected cellulitis with potential abscess.

The patient returns a week later with no improvement on Keflex® and Bactroban.™ The wound/abscess on her left dorsal hand is erythematous, tender, and warm to touch; it measures 1.8 x 1 cm in size with a new 1 cm induration noted at the wound bed (see Fig. 2). At this office visit, an incision and drainage of the abscess on her left dorsal hand is performed, yielding purple-yellow pus. A wound culture is obtained, and she is started on doxycycline in addition to the Keflex®.

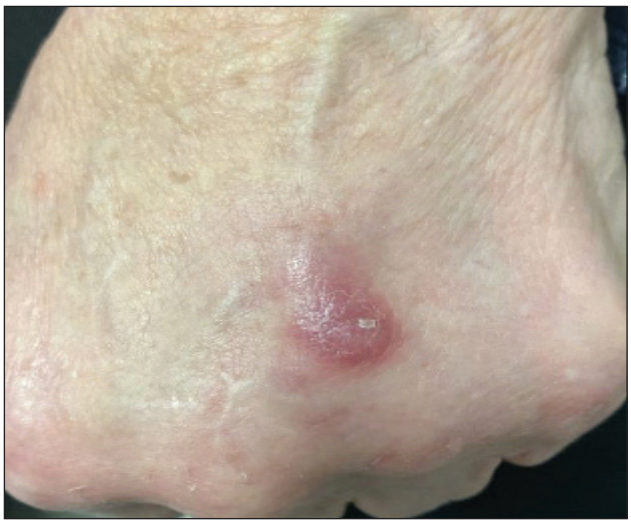

Fig. 1. Patient's sore, day 10, as first presented in office.

The patient presents back in the office two weeks later with no improvement in her left-hand abscess after finishing a seven-day course of doxycycline. Her left hand has an erythematous maculopapular lesion measuring approximately 1.8 x 2 cm in size that is not draining but is tender (see Fig. 3). An e-consult with Infectious Diseases is initiated after which the patient is prescribed rifampin 300 mg oral daily and clarithromycin 500 mg oral two times a day for six weeks.

Three weeks later the patient calls into the office reporting the abscess is not any smaller, although it is also not as red, swollen, or tender. It is not responding to rifampin and clarithromycin and is now persistently draining purulent fluid. Exam of the patient's left dorsal hand reveals a tender, round, erythematous/violaceous, maculopapular lesion that measures approximately 2 x 2.5 cm in size with a small open area draining a scant amount of serosanguinous fluid (see Fig. 4). At this visit, she is instructed to continue rifampin and clarithromycin therapy for three more weeks; an urgent referral is placed to Dermatology for potential biopsy and further recommendations.

That same week, the patient is seen by Dermatology for tangential biopsy. She later messages into the office to report her wound is constantly draining from the biopsy site.

QUESTIONS

1. What is the differential diagnosis for this patient?
2. What are the signs and symptoms of cellulitis?
3. Who is at risk for cellulitis?

4. What are the most common microbial pathogens in cellulitis?
5. What is the difference between cellulitis and an abscess?
6. How does the treatment differ between cellulitis and an abscess?

ANSWERS

1. Potential diagnoses include but are not limited to cellulitis of the dorsal hand, simple cutaneous abscess, infected insect/animal bite, retained foreign body, ruptured/infected epidermal inclusion cyst, contact dermatitis, atopic dermatitis, tinea corporis, and squamous cell carcinoma.
2. Symptoms of cellulitis include erythema, edema, warmth, and pain, and patients may present with purulent drainage and fever.
3. Most middle-aged and older adults who experience a disruption in their skin barrier because of injury are at higher risk of developing cellulitis. Patients who have a history of obesity, eczema, psoriasis, venous insufficiency, immunosuppression, diabetes, and/or pre-existing skin infection are at higher risk of developing cellulitis if there is a break in the skin barrier.
4. The most common pathogens in cellulitis are beta-hemolytic streptococci (groups A, B, C, G, and F), *Streptococcus pyogenes*, *Staphylococcus aureus*, and methicillin-resistant *Staphylococcus aureus* (MRSA).
5. Patients with cellulitis may or may not present with an abscess. A skin abscess is a collection of pus that is fluctuant, often with an erythematous nodule.
6. Patients who present with cellulitis should be started on antibiotics that will cover the suspected pathogen. Initial antibiotics for cellulitis should cover beta-hemolytic streptococci. If a patient presents with purulent wound drainage, toxic symptoms (fever >100.5°F, hypotension, tachycardia), or has recently been hospitalized or resides in a long-term care facility, antibiotics for MRSA coverage may be warranted.

   Patients who present with an abscess should undergo incision and drainage. After draining an abscess, antibiotics are not typically warranted because incision and drainage is the definitive treatment; however, if the patient is experiencing severe local infection or systemic symptoms, fails to respond to initial antibiotic, or has experienced an animal bite, they may be started on antibiotics after

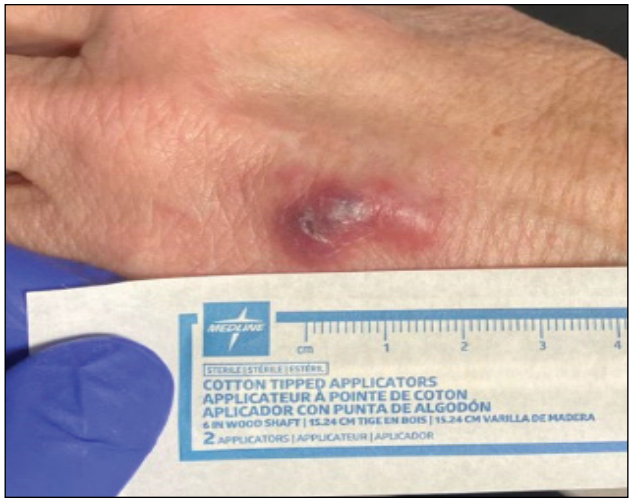

Fig. 2. Patient's sore at second visit, a week later, showing no improvement on Keflex® and Bactroban™.

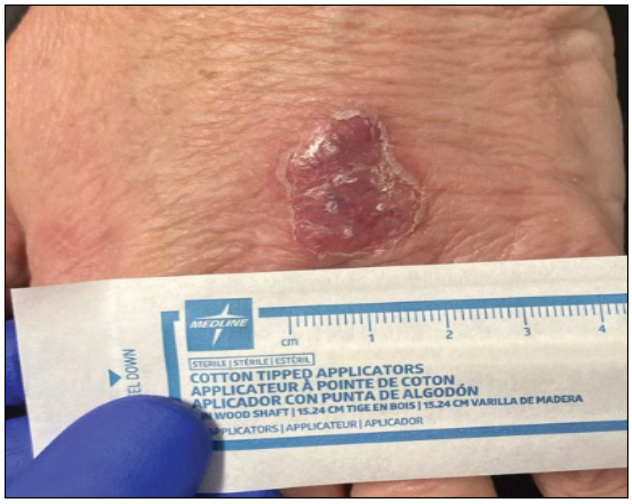

Fig. 3. Patient's sore, two weeks post-drainage, showing no improvement after a seven-day course of doxycycline.

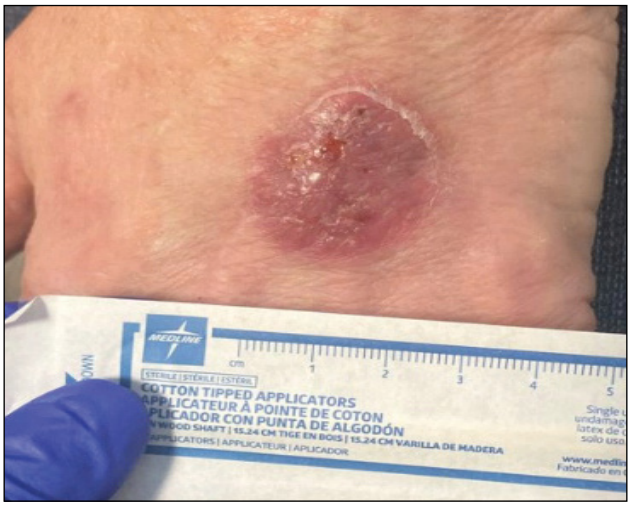

Fig. 4. Patient's sore, five weeks post-drainage, showing no improvement on rifampin and clarithromycin.

undergoing an incision and drainage. Additionally, patients who are immunocompromised or extremely young or old should be started on antibiotics after an incision and drainage.

ADDITIONAL CASE HISTORY

The wound culture grows *Tsukamurella tyrosinosolvens* but the lesion does not respond to doxycycline, rifampin, or clarithromycin. Biopsy results show giant cells, and staining is positive for herpes simplex virus 1 and 2. The immunostains suggest an old herpes virus infection, and thus the patient is started on Valtrex™ and minocycline by her dermatologist. Minocycline is shortly discontinued by her Infectious Diseases specialist due to low suspicion that this is a bacterial infection, and Valtrex™ is increased to 1 gram every eight hours for two weeks.

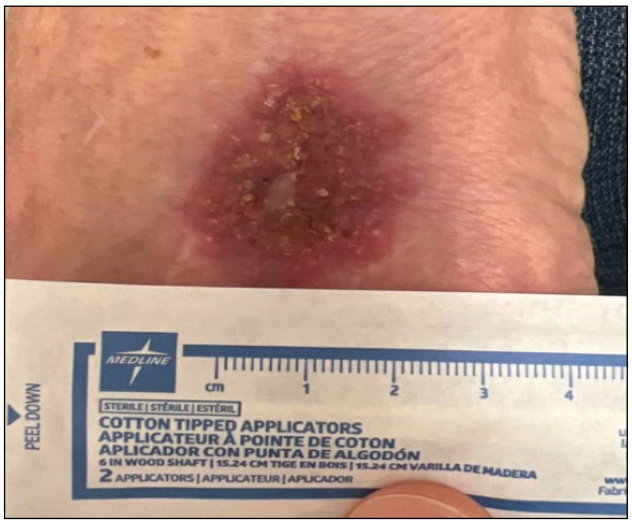

Fig. 5. Patient's sore showing improvement, eight weeks after initial visit and two weeks after initiation of Valtrex™.

Two weeks later, the patient reports her left-hand lesion is finally starting to improve (see Fig. 5). If the wound had not improved after the additional week of Valtrex™, minocycline could have been added.

DISCUSSION

Herpes simplex should be considered in any case of a new painful cutaneous lesion, especially those that leak pustular fluid. Testing can include Tzank smear, but polymerase chain reaction testing is more readily available. Treatment with acyclovir or valacyclovir as early in the course of disease as possible is recommended for 10 days and possibly longer depending on reassessment.

Tsukamurella tyrosinosolvens is a rare Gram-positive acid-fast bacillus that belongs to the class *Actinomycetes*. These bacteria are found in soil and water and may be an opportunistic pathogen that particularly affects immunocompromised individuals and those with indwelling medical devices (peripherally inserted central catheter lines, cardiac pacemaker implants, etc.).[1]

Tsukamurella are very similar to other species such as *Rhodococcus*, *Goronia*, *Corynebacterium*, *Nocardia*, and *Mycobacterium*.[2,3] The most effective treatment strategy is starting appropriate antibiotics quickly and, if it is thought to be a device-associated infection, removing the indwelling medical device during antibiotic therapy.[2]

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SPOTLIGHT ON CLINICAL RESEARCH

Clinical Studies at LG Health

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Small


Madara

This Spotlight on Research highlights the currently enrolling research studies being conducted by the LG Health Research Institute. To learn more about all research studies at Penn Medicine Lancaster General Health, visit iConnect by scanning the QR code at right.

ALZ-NET

Alzheimer's Association / "Alzheimer's Network for Treatment and Diagnostics (ALZ-NET)" registry: aims to collect data from individuals who are evaluated for, or receive treatment with, novel (or new) FDA-approved therapies for Alzheimer's disease (AD) — *Sponsor: Alzheimer's Association · Principal Investigator: Matthew Beelen, MD · Sub-Investigator: Connie Metzler, RN · Study Coordinators: Natalie Maston, Annmarie Blair, LouAnne Kruse*

The research team at LG Health is enrolling in the Alzheimer's Network for Treatment and Diagnostics (ALZ-NET) Registry sponsored by the Alzheimer's Association. This registry explores long-term safety, along with clinical use and outcomes for patients being evaluated for or treated with novel FDA-approved therapies for Alzheimer's disease. Enrollment in this registry has been highly successful due to the strong efforts of the investigators and study coordinators. Patients and their legally authorized representatives have expressed great interest in this registry as it will contribute to the advancement of treatments for Alzheimer's disease that may benefit their children, grandchildren, and all future generations.

BACKBEAT

BradycArdia paCemaker with AV interval modulation for Blood prEssure treAtmenT — *Sponsor: Orchestra Biomed · Principal Investigator: Jeffrey Arkles, MD · Sub-Investigators: Sandeep Bansal, MD; Matthew Bernabei, MD; R. Ward Pulliam, MD; Stacy Eshleman, CRNP; Laura Koonce, CRNP; Nicole Newman, CRNP; Jill Schaeffer, CRNP · Study Coordinators: Sarah Stuart, Andy Hershey*

This is a prospective, multinational, randomized, double-blind, clinical trial evaluating the safety and effectiveness of a novel atrioventricular interval modulation (AVIM) algorithm downloaded into a dual-chamber Medtronic Astra/Azure pacemaker. Patients scheduled to undergo implantation of a de novo Astra/Azure pacemaker system — and those who already have one implanted — may be screened for inclusion into this study if they also have uncontrolled hypertension. All eligible subjects will receive the AVIM RAMware and be randomized 1:1 to either have AVIM therapy turned On or turned Off. All subjects will continue to receive antihypertensive drug therapy.

The study team has experienced some challenges with enrollment due to the study's strict eligibility criteria. This makes it difficult to find patients who qualify for the study. The current blood pressure treatments used are effective and well managed, which also limits the number of eligible patients.

CARDIO-TTRansform OLE

An Open-Label Extension Study to Assess the Long-Term Safety of Eplontersen (ION-682884) in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy (ATTR-CM) — *Sponsor: Ionis Pharmaceuticals · Principal Investigator: Tareck Nossuli, MD · Sub-Investigators: Arpan Patel, DO; Roy Small, MD; Amit Varma, MD; Michael Viray, MD · Study Coordinators: LouAnne Kruse, Kay Knepper*

Ionis Pharmaceuticals, in collaboration with Akcea Therapeutics, is sponsoring a multicenter, double-blind study, referred to as CARDIO-TTRansform, to evaluate the efficacy of AKCEA-TTR-LRx. This drug is a second-generation RNA-targeted therapy designed to inhibit TTR production. The study randomized participants to receive subcutaneous injections of either the study drug, AKCEA-TTR-LRx, or placebo. In early 2024, the study

sponsor invited sites to join the open-label extension (OLE) study, which is open to people who participated in the CARDIO-TTRansform study. The two participants enrolled in CARDIO-TTRansform at Lancaster General Hospital (LGH) were invited to join the OLE. Participation in the OLE begins after participants have completed their end-of-study visit for CARDIO-TTRansform and extends for up to 3.7 years. All participants in the OLE receive the study drug eplontersen and go through a screening period (up to 10 weeks), treatment period (up to 36 months after screening period), and post-treatment period (six months after end-of-treatment period).

DCM-DETECT

Dilated Cardiomyopathy Detection using AI and screening with mobile Technology — *Sponsor: Investigator-Initiated Study · Principal Investigator: Roy Small, MD · Sub-Investigators: Tareck Nossuli, MD; Arpan Patel, DO; Amit Varma, MD; Michael Viray, MD; Douglas Gohn, MD · Study Coordinators: Natalie Maston, Brianna Triplett*

The DCM-DETECT study utilizes an AI-enhanced mobile 6-lead EKG to detect undiagnosed dilated cardiomyopathies (DCM) in family members of patients with DCM. In this study, probands (the first family member identified with a non-ischemic DCM) will be recruited and asked to provide family medical history, complete a 6-Lead EKG using a mobile EKG device, contact their first-degree relatives (FDRs) to invite them to join the study, and complete a survey. FDRs who choose to participate will also complete the mobile 6-Lead EKG and survey. In addition, they will be encouraged to obtain a transthoracic echocardiogram (TTE) through their health care provider. The primary objective of the study is the uptake of screening TTEs in FDRs of patients with DCM compared to historical controls. The study is also recruiting at the Central Pennsylvania Clinic (CPC), which cares for Amish and Old Order Mennonite populations. At this site the added goal is to study the application of advanced technology in a rural, underserved population.

Enrollment at LG Health has been successful, with 28 probands enrolled. Of these, 10 have successfully recruited some or all their FDRs, resulting in a total of 11 FDRs enrolled at LG Health. At CPC, five probands have been enrolled, all of whom have successfully recruited their FDRs, contributing to a total of 20 FDRs enrolled, with still more expected to enroll. Due to the larger family sizes within the Amish and Old Order Mennonite populations seen there, the proband-to-FDR ratio at CPC is significantly higher than at LG Health.

EMPOWER

Assessment of the Carillon Mitral Contour System® in Treating Heart Failure with Functional Mitral Regurgitation — *Sponsor: Cardiac Dimensions · Principal Investigator: Rupal Dumasia, MD · Sub-Investigators: T. Raymond Foley, MD; Rahul Jhaveri, MD; Arpan Patel, DO · Study Coordinators: Andy Hershey, LouAnne Kruse*

The objective of this prospective, randomized, blinded clinical trial is to assess the safety and efficacy of the Carillon Mitral Contour System® in treating heart failure with functional regurgitation (FMR). Eligible patients must have symptomatic heart failure with functional mitral regurgitation; be NYHA class II, III, or IV; have left ventricular EF ≤50%; and meet the study's six-minute walk test requirements. Participants are randomized to either the study group and receive the study device or to the control group, whose members receive no device.

The study team follows the participants at set intervals until 24 months post-randomization, at which point everyone is unblinded. All participants will continue to be followed annually for three years after unblinding. The enrollments for this study had a slower start due to the effectiveness of current heart failure therapy. Enrollment is improving as practitioners recognize the potential benefits of this heart failure modifying treatment.

LeAAPS

Left Atrial Appendage Exclusion for Prophylactic Stroke Reduction Trial — *Sponsor: AtriCure · Principal Investigator: Jeremy McGarvey, MD · Sub-Investigators: Mark Epler, MD; Alexander Bridges, MD; Robert Wenger, MD · Study Coordinators: Lynsey Jones, Andy Hershey, Sarah Stuart, Molly Clifford*

The objective of this trial is to evaluate the effectiveness of left atrial appendage exclusion (LAAE) for the prevention of ischemic stroke or systemic arterial embolism in subjects undergoing cardiac surgery who have risk factors for atrial fibrillation (AF) and ischemic stroke. The AtriClip is FDA approved for use in patients with AF, but the use of it in patients without diagnosed AF is investigational. Participants can expect their participation to last for about five years from enrollment to study end.

Enrollment at LGH for this study continues to be successful. The study team exceeded its initial enrollment goal of 100 patients and has consistently ranked within the top 10 enrolling sites study-wide since study initiation.

Left vs. Left RCT

Cardiac Resynchronization Therapy Using His/Left Bundle Branch Pacing vs. Biventricular Pacing with a Left Ventricular Epicardial Lead in Patients with Heart Failure with Left Ventricular Ejection Fraction ≤50% and with either a Wide QRS Complex (>130 ms) or with/anticipated >40% Pacing Randomized Clinical Trial — *Sponsor: Baylor College of Medicine · Principal Investigator: Matthew Bernabei, MD · Sub-Investigators: Sandeep Bansal, MD; Jeffrey Arkles, MD; R. Ward Pulliam, MD · Study Coordinators: Andy Hershey, Sarah Stuart*

This trial compares the effects of His or left bundle branch pacing (LBBP) to biventricular pacing (BiVP) on quality of life, exercise capacity, hospitalization for heart failure, and mortality in patients with heart failure and conduction system disease. Patients are randomized 1:1 to one of two pacing therapy arms: His/LBBP or BiVP using any commercially available leads and devices.

The enrollment goal at our site was 34 participants. Challenges to enrollment center around LBBP being the preferred treatment option among most patients and physicians. As a result, many patients are hesitant to join the study since there is a chance they may be randomized to receive BiVP instead of LBBP. For many physicians, LBBP is seen as preferrable due to the lower cost, shorter procedure time, and perceived lower risks. However, enrollment efforts remain ongoing as this is the seminal randomized clinical trial comparing LBBP to traditional BiVP to determine which therapy is most effective.

Lp(a) EZEF – ACCLAIM

A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Investigate the Effect of Lepodisiran on the Reduction of Major Adverse Cardiovascular Events in Adults with Elevated Lipoprotein(a) who have Established Atherosclerotic Cardiovascular Disease or Are at Risk for a First Cardiovascular Event — *Sponsor: Eli Lilly · Principal Investigator: Marjan Mujib, MD · Sub-Investigator: Joette Hughes, CRNP · Study Coordinator: Kay Knepper*

The purpose of this study is to evaluate the efficacy of lepodisiran, a small interfering RNA, in reducing cardiovascular risk in participants with high lipoprotein(a) who have cardiovascular disease or are at risk of a heart attack or stroke. Study participants are randomized to receive either the study drug or a placebo. Participation lasts about five years and includes a Screening Period, Study Treatment Period, and Final Visit. Although one study arm closed to enrollment shortly after our site was activated to begin the study, the study team has enrolled 12 of the 20 participants set as the enrollment goal. The success in enrollment can be attributed to the pre-existing relationships between the study investigators and the patient population.

PACeS

Anticoagulation for New-Onset Post-Operative Atrial Fibrillation (POAF) after CABG — *Sponsors: CT Surgical Trials Network Research Group; National Heart, Lung, and Blood Institute (NHLBI) · Principal Investigator: Mark Epler, MD · Sub-Investigators: Alexander Bridges, MD; Jeremy McGarvey, MD; Robert Wenger, MD · Study Coordinators: Lynsey Jones, Andy Hershey*

The primary objective of this prospective, open-label, randomized study is to evaluate the effectiveness (prevention of thromboembolic events) and safety (major bleeding) of adding oral anticoagulation (OAC) to background antiplatelet therapy in patients who develop new-onset POAF after isolated coronary artery bypass graft (CABG) surgery. This trial randomizes participants (1:1 ratio) to receive OAC (intervention arm) or no OAC (control arm). Eligible patients who choose not to participate may enroll in a parallel registry instead.

The study team successfully enrolled 14 participants into this study. They continue to screen, but many patients do not develop AF post-operatively at LGH. The study coordinators have a strong relationship with the Lancaster General Health Physicians Cardiothoracic Surgery team, from the physicians and advance practice providers to schedulers and administrative staff. The team is dedicated to the success of this study and will continue to screen for eligible patients while the study remains open.

PSR-APV

Product Surveillance Registry — *Sponsor: Medtronic · Principal Investigator: Meghan Dermody, MD · Sub-Investigator: John Affuso, MD · Study Coordinators: Brianna Triplett, Jordan Lapp*

The Product Surveillance Registry (PSR) collects data about the safety and effectiveness of Medtronic products on the market. The original registry has been active for many years, but there are multiple cohorts under the PSR umbrella. LG Health received approval to enroll participants in two of the cohorts: Aortic and Arteriovenous (AV) Access. The AV Access cohort of the study has been closed to enrollment by the sponsor. The study team at LG Health enrolled 37 participants into this cohort and was recognized as the top enrolling site in the Fall of 2023, prior to enrollment closure. The Aortic cohort remains open to enrollment.

REAL-AF Registry

Real-world Experience of Catheter Ablation for the Treatment of Symptomatic Paroxysmal and Persistent Atrial Fibrillation Using Novel Contact Force Technologies — *Sponsors: Biosense Webster; Heart Rhythm Clinical and Research Solutions, LLC (HRCRS) · Principal Investigator: Sandeep Bansal, MD · Sub-Investigators: Jeffrey Arkles, MD; Matthew Bernabei, MD; Stacy Eshleman, CRNP; Jill Martin, CRNP; Nicole Newman, CRNP; Jill Schaeffer, CRNP · Study Coordinators: Andy Hershey, Jordan Lapp*

This registry aims to collect real-world clinical experience of Paroxysmal (PAF) and Persistent (PsAF) Atrial Fibrillation ablation radiofrequency technologies. The study team collects data at pre-ablation, during the procedure, and at 10-12 weeks, six months, and one year post-ablation. Data from the registry will be used to assess the effectiveness and long-term safety of the technologies.

Enrollment at LG Health was very successful for the first two years. Any patient who was scheduled for a standard of care (SOC) pulmonary vein isolation (PVI) was screened for the registry. In September 2024, there was a change in SOC — radiofrequency PVI procedures were largely replaced with pulsed field ablations. The sponsor updated the registry protocol to include these procedures using their equipment, however the LG Health team had adopted equipment from an alternative device company. In June 2025, however, Biosense Webster equipment was approved for use at LG Health. The investigators will use this equipment and determine if they will continue using it or return to the equipment previously in use.

ROADSTER 3

Post-Approval Study of Transcarotid Artery Revascularization in Standard-Risk Patients with Significant Carotid Artery Disease and ROADSTER 3 Extended Follow-up Sub-Study — *Sponsor: Boston Scientific · Principal Investigator: Meghan Dermody, MD · Sub-Investigators: John Affuso, MD; Thomas O'Connor, MD; Todd Wood, MD · Study Coordinators: Kay Knepper, LouAnne Kruse*

This open-label, multicenter, single-arm, prospective post-approval study evaluates the ENROUTE Transcarotid Stent System when used with the ENROUTE Transcarotid Neuroprotection System. The study will explore the treatment of patients at standard risk for adverse events from carotid endarterectomy who require carotid revascularization and meet the study eligibility criteria.

The sponsor planned to enroll a maximum of 400 patients at up to 65 U.S. and EU sites. At LG Health, the study team enrolled eight participants, five of whom have consented to participate in the ROADSTER 3 Extended Follow-up Sub-Study, which extends long-term follow-up from one year post-procedure to five years post-procedure. The remaining three participants are anticipated to join the Follow-Up Sub-Study when they complete their participation in the main study. This extended follow-up period is expected to provide long-term outcomes for these participants who were treated with the ENROUTE Transcarotid Stent System and ENROUTE Transcarotid Neuroprotection System.

THRIVE

A Pivotal, Prospective, Multicenter, 2:1 Randomized, Double-Blind, Controlled Study Comparing the THerapeutIc IntraVasculaR Ultrasound (TIVUS™) REnal Denervation System vs. Sham for the Adjunctive Treatment of Hypertension — *Sponsor: SoniVie · Principal Investigator: Rupal Dumasia, MD · Sub-Investigators: Jian Shan, MD; Dean Campbell, MD; David Somerman, DO · Study Coordinators: Lynsey Jones, Sarah Stuart, Kay Knepper, LouAnne Kruse, Brianna Triplett*

The primary objective of the THRIVE Pivotal study is to demonstrate the adjunctive effectiveness and safety of the TIVUS™ renal denervation system in people with hypertension. THRIVE is a double-blind, sham-controlled study in which participants are randomized 2:1 to the treatment group using the TIVUS™ system or to the sham group. Patients who may be eligible will go through multiple eligibility visits to ensure they qualify for the study after signing the consent form. If they are still eligible after the screening period, they will be randomized. In order to maintain the double-blind, all patients will undergo a procedure. However, the sham procedure will be minimally invasive so participants are not put at increased risk.

All participants will stop taking any blood pressure medications during the screening period through two months post-procedure. After that, participants with uncontrolled hypertension will be put back on antihypertensive medication. Participants will be unblinded at the six-month study visit. At that time, any participants who are in the sham group who have uncontrolled blood pressure can cross over to have the renal denervation procedure performed.

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TOP TIPS FROM FAMILY PRACTICE

Measles, Allergies, Gout, Flu

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EXPERTS WARN MEASLES COULD BECOME ENDEMIC

Five years ago, health experts declared measles had been eliminated from the United States, thanks to an ambitious measles-mumps-rubella (MMR) vaccination program for children.[1] But as vaccination rates decline, measles is making a comeback. As of mid-August, the Centers for Disease Control and Prevention (CDC) noted 1,356 reported cases of measles in the nation this year.[2]

Now, a study from Stanford suggests measles could become endemic again[3] because measles is so contagious — one of the most infectious diseases in the world. Estimates show that someone with measles will infect 12-18 others, on average. By comparison, someone with COVID-19 can infect about three people, on average.

The CDC recommends two doses of MMR vaccine for children, starting with a first dose at 12-15 months of age and a second dose at 4-6 years of age. In areas near a measles outbreak, however, babies may be able to get vaccinated as early as 6 months of age.

Some adults may need to get vaccinated too. Adults are generally considered fully vaccinated if they received two doses of MMR or MMRV. If born before 1957, they are presumed to be immune due to widespread measles exposure during that time. If a patient received the inactivated measles vaccine between 1963 and 1967, however, they may need a booster and may seek consultation.

FDA ISSUES CETIRIZINE/LEVOCETIRIZINE WITHDRAWAL SYNDROME WARNING

The Food and Drug Administration (FDA) issued a Drug Safety Communication requiring new warnings about the rare but severe pruritus that can occur when patients discontinue the oral allergy medications cetirizine (Zyrtec®) or levocetirizine (Xyzal®) after long-term use.[4] Both medications are second-generation antihistamines approved for treating seasonal rhinitis, perennial allergic rhinitis, and chronic idiopathic urticaria. The median time to onset of pruritus after medication discontinuation was 2 days, with a range of 1-5 days. In 92% of cases where usage duration was reported, patients had used the medications for more than three months before experiencing withdrawal symptoms.

Of the 93 cases where patients reported attempting to restart and stop the medication(s), pruritus occurred in 92. However, restarting the medication(s) resolved symptoms in 71 of 79 individuals (90%), and tapering after restarting resolved symptoms in 9 of 24 patients who attempted this approach. Data suggest that longer medication use may increase the risk of a discontinuation reaction, as "the number of pruritic cases increases with duration of use."

For health care professionals, the FDA recommends discussing discontinuation risks with patients — especially those planning to take these medications long term — and encouraging patients to report severe itching after stopping.

FIVE THINGS TO KNOW WHEN TREATING GOUT[5]

The following are recommendations for clinicians treating patients with gout:

1. It's possible that a patient may have some kidney damage from taking anti-inflammatory medications. Thus, for an acute attack of gout, consider that many rheumatologists use prednisone as a first-line treatment.
2. If prescribing prednisone, start with 40 mg/d for four days, then taper down to 30 mg/d for four days, 20 mg/d for four days, and continue to reduce in that fashion.
3. Clinicians should not start patients on allopurinol during an acute attack — allopurinol does not treat acute attacks. It is helpful in lowering uric acid levels in the blood, and is useful for prevention and management, but patients should start allopurinol after an acute attack of gout has settled. For patients who are already on allopurinol, however, they can continue taking their medication without adjusting the dose. Simply treat the acute attack.

4. Check the fingers for tophi.
5. Patients who have tophi may not be able to feel it. A dual-energy computed tomography (DECT) scan may help differentiate between gout and pseudo gout.

ONE DOSE OF BALOXAVIR CUTS FLU TRANSMISSION

Findings from a large multicountry trial, published in *The New England Journal of Medicine,* demonstrated that treatment with a single oral dose of baloxavir marboxil significantly reduced influenza transmission from infected individuals to close contacts.[6]

Baloxavir has shown efficiency as treatment and post-exposure prophylaxis for influenza. Baloxavir was shown to rapidly reduce influenza virus titers and stop shedding of infectious virus faster than oseltamivir, suggesting it can reduce transmission.

Most individuals in the trial had influenza A — H3N2 or H1N1 pdm09 — infections, while 20% had influenza B infections. By day 5, laboratory-confirmed influenza transmission was significantly lower in households where index patients received baloxavir compared to placebo.

The availability of an antiviral drug for influenza A and B with dual treatment effects on illness and transmission is a welcome addition to the overall strategy for influenza control. Although vaccines will remain the primary control measure for influenza epidemics and pandemics, antiviral drugs play a complementary role, particularly in a pandemic scenario, as well as in persons who are not vaccinated seasonally.

Choosing Wisely

Originally published in the Fall 2015 issue of JLGH *in conjunction with the American Board of Internal Medicine's now-complete Choosing Wisely campaign, this edited reprint is offered to remind physicians of the importance of talking with patients about what tests, treatments, and procedures are needed — and which ones are not.*

RECOMMENDATIONS FROM THE SOCIETY OF HOSPITAL MEDICINE — ADULT HOSPITAL MEDICINE

❶ **Don't place (or leave in place) urinary catheters for incontinence or convenience or monitoring of output for non-critically ill patients.** To monitor diuresis, weigh the patient instead. Acceptable indications for a catheter are critical illness, urinary obstruction, hospice care, or perioperative use (for less than two days) for a urologic procedure. Published guidelines suggest that hospitals and long-term care facilities should develop, maintain, and promulgate policies and procedures for catheter insertion, including recommended indications, insertion and maintenance techniques, discontinuation strategies, and replacement indications.

❷ **Don't prescribe medications for prophylaxis of stress ulcer in medical inpatients unless they are at high risk for GI complications.** Evidence-based guidelines do not support their use for adult patients in non-ICU settings. Both histamine-2 receptor antagonists and proton-pump inhibitors are associated with adverse drug events and increased costs. Community-acquired nosocomial pneumonia and *Clostridium difficile* susceptibility can be enhanced by these drugs.

❸ **Avoid transfusions of red blood cells for arbitrary hemoglobin or hematocrit thresholds in the absence of symptoms of active coronary disease, heart failure, or stroke.** The American Association of Blood Banks recommends adhering to a restrictive transfusion strategy (7-8 g/dL) in hospitalized, stable patients and suggests that transfusion decisions be influenced by symptoms as well as by hemoglobin concentration.

❹ **Don't order continuous telemetry monitoring outside of the ICU without using a protocol that governs their continued use.** In patients with low-risk cardiac chest pain and a normal electrocardiogram, telemetric monitoring has limited utility or measurable benefit. Published guidelines for its use provide clear indications that are contingent upon the frequency, severity, and duration of symptoms, as well as the conditions under which they occur. Inappropriate use is likely to increase the cost of care, while potentially producing falsely positive findings that can lead to errors in patient management.[7]

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General Medical Practice in America

A Brief History

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Editor's note: In this issue of JLGH, *we kick off a series of articles by Dr. Zervanos on the circumstances, institutions, and people who built the medical community now recognized as Penn Medicine Lancaster General Health. Much of the information comes from manuscripts he authored and donated to the American Association of Family Physicians Foundation. This first installment offers a brief history of general medical practice in the United States.*

European migrants relied on Native Americans and their knowledge of the medicinal value of certain plants to manage their various ailments.[1] Eventually, many different practitioners, who could provide some level of health care, migrated to the colonies, but there were few physicians among them. This was because it took 14 years of education for an English or French physician to attain a medical degree. Thus, it would have required an adventurous spirit and strong economic or political incentives for physicians to migrate and accompany the early settlers to America.[2]

It was not until the end of the 17th century that American settlements would have significant numbers of health care practitioners. Besides the relatively few educated physicians from European universities, there were barber-surgeons, apothecaries, midwives, folk practitioners, and minister-physicians, as well as a growing number of apprentice-trained practitioners with knowledge of surgery and compounding pharmaceuticals.[1] The educated physicians and their apprentices were referred to as the "regulars." By the mid-18th century, of the estimated 3,500 to 4,000 regular physicians, fewer than 400 had received formal medical training, and even then, not all held medical degrees; the vast majority were apprentices.[3]

Dr. John Morgan (left) and Dr. William Shippen, Jr. (right) founded America's first medical school in Philadelphia. *Morgan portrait by Angelica Kauffman (1741-1807); Shippen portrait by Charles Willson Peale (1741-1827).*

In 1765, Drs. John Morgan and William Shippen, Jr. founded the first medical school in America at the College of Philadelphia, now known as the Perelman School of Medicine at the University of Pennsylvania.[4] Early schools also included Columbia in New York and Harvard in Massachusetts; these were influenced by the European medical school model, particularly that of the University of Edinburgh.

Although many of the medical practitioners were apprentice trained and met the standards of the time, the demand for medical professionals exceeded the ability of these early schools to graduate clinicians. Medical education could be a lucrative enterprise, so with few regulations and no real standards, enterprising physicians with rhetorical skills and sufficient backing could establish their own medical schools.

The entrance requirements to most schools were minimal. Not every student was expected to be able to read and write, nor to have a "normal school" education. Most importantly, they needed to be able to pay the fees and agree to attend the lectures. To acquire clinical experience, students were also expected to apprentice with a physician.[5]

Respected members of the profession advocated for improved academic standards and for state governments to enforce strict licensing requirements, but these efforts met with little success, as these physicians were considered elitists who were self-serving and feared competition. In 1847, the American Medical Association (AMA) was formed to bring about needed reforms.

Unfortunately, hundreds of schools had already been established with varying degrees of attention to the quality of education being offered, producing physicians with varying degrees of quality and skill. What

ultimately defined a "good doctor" may have depended as much on the internal drive of the student as it did on the school from which they had graduated.[3] Many of the physicians graduating from proprietary schools were no better than less formally trained practitioners who simply claimed they were doctors.

During the Jacksonian era (approximately 1820-1840), the sentiment included a distrust of elitists, and whatever regulations or licensing requirements may have been in place were dispensed with or allowed to lapse, such that egalitarianism prevailed and quackery medicine went ungoverned. Among the "irregular" schools of thought that burgeoned at the time were:

- The Thomsonians, inspired by Samuel Thomson (1769-1843), who relied on herbs along with heat, ritual baths, emetics, purgatives, and diuretics.
- The Homeopaths, acolytes of the German physician Samuel Hahnemann (1755-1843), who relied on pharmaceuticals made of highly diluted solutions and powders that often produced effects — when used at full strength — similar to the diseases they were intended to cure.
- The Eclectics, who relied on botanicals, mineral remedies, or a combination of Allopathic, Thomsonian, and Homeopathic practices, or whatever was thought to work.[1]

The Library and Surgeon's Hall — part of the medical school at the College of Philadelphia — was used for lectures between 1765 and 1801.

Although practitioners, both regulars and irregulars, were expected to conduct themselves ethically, they often made matters worse, for example, by using drugs containing arsenic or mercury, or by employing procedures such as bleeding and cupping.[3]

Much can be said of the many respected members of the profession who advocated for improved academic and professional standards. Among them were Drs. Samuel Humes and John Light Atlee of Lancaster, who founded the Lancaster City and County Medical Society in 1844, and Dr. Nathan S. Davis, who in 1847 played a leading role in the development of the AMA. These men advocated for the much-needed reforms in medical education and insisted that state governments enforce strict licensing requirements. Dr. Davis became the AMA's first president, and Dr. Atlee assumed that role in 1883.

It wasn't until the post-Civil War era that thousands of Americans chose to acquire their medical education in the great medical centers of Europe. Many of these newly minted medical scientists returned to the United States, entered the academic medical community, and gained the public's respect and support for major medical education reforms. By 1876, schools that aspired to meet these burgeoning standards joined together to form the Association of American Medical Colleges.[6]

In 1893, a new medical school became fully integrated with the newly established Johns Hopkins University. The medical school was to be governed by the university and abide by its high academic standards. Students were required to have earned an undergraduate degree with pre-medical preparation in biology and chemistry, and to undergo a four-year medical school curriculum that included the basic sciences, laboratory research, and clinical experiences, along with bedside teaching and supervision.[1]

In 1904, Lancaster-born John Herr Musser, MD (1856-1912), a professor at the University of Pennsylvania, became president of the AMA. During his tenure, the Council on Medical Education was established; its members introduced the categorization of medical schools according to a grading system. The AMA had gained sufficient credibility, influence, and authority to institute significant changes and accredit medical schools, and the AMA commissioned Abraham Flexner, PhD, a highly esteemed educator, to visit and critique all 160 medical schools in the United States and Canada.

In 1910, Dr. Flexner published his findings in what came to be known as the "Flexner Report." Using

the AMA's grading system and the Hopkins school as the ideal model, the medical schools were categorized into four groups.[7] Even the best schools had to make changes, and grants were provided to schools willing and able to do so.

U.S. medical schools had to meet standards to be accredited by the AMA Council of Medical Education. The AMA, which submitted its report to every state licensing board, recommended that those schools unable to meet minimum standards be forced to close. Some chose to merge, and nearly all came under the governance of a university.[8]

By 1920, as the Flexner reforms were fully implemented, only 66 schools remained accredited. Dr. Flexner's reforms also recommended that every medical school graduate complete a one-year internship approved by the AMA, and thus Lancaster General Hospital developed an AMA-approved internship program soon after Flexner's recommendations.[9] Completion of an internship as well as the passing of a state licensing exam became the new standard for licensure to practice in Pennsylvania.

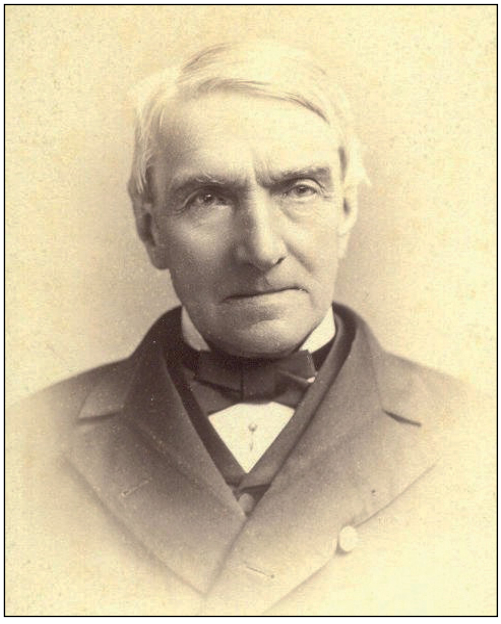
With the rapid advancements in medical science and technology, many physicians became self-declared specialists and formed specialty societies to benefit from each other's expertise. Yet, formalized residency training beyond the internship, and subsequent board certification, did not occur until 1916, when ophthalmology became the first specialty to establish a board. By 1940, an additional 16 specialty boards had formed.[10]

There was a strong economic incentive to become a specialist, as specialists were able to garner higher fees. Moreover, the rise of the third-party insurance system gained momentum in the 1930s, as it not only covered the cost of hospitalized patients but also paid the fees for services provided by specialists.[11]

As the public became more informed, there was an increasing demand for specialized care. The demand, coupled with the added financial incentives, led most medical school graduates to choose specialty training. Consequently, by the 1950s, the general practitioner was fast disappearing, as less than half of the physicians in America were general practitioners and were not being replaced. This meant that many people, especially in rural America, were faced with limited or no access to a physician.[12]

With strong leadership from the newly formed American Academy of General Practice (AAGP), in concert with the AMA's Council on Medical Education, a two-year residency in General Practice was instituted in 1950. Unfortunately, these programs lacked the prestige of a specialty, and in most cases, they were not much more than an additional year of internship, garnering graduates of this system little respect from the academic medical community and attracting few candidates.

In 1961, Kerr White, MD, who coined the term "primary care physician," and his colleagues, T. Frank Williams, MD, and Bernard G. Greenberg, PhD, published their classic study on the "Ecology of Medical Care," which described three levels of care, underscoring the principal role of the primary care physician. Their study helped support the argument that the "primary care physician" is central to delivering health care and can manage the vast majority of a patient's comprehensive care needs.[13] This study gave credence to the argument that more attention should be given to the education of generalists and the development of a primary care specialty.



Dr. John Light Atlee co-founded the Lancaster City and County Medical Society and was president of the AMA from 1883-1884. *Cabinet card by B. Frank Saylor (d. 1920).*

AAGP leaders continued to define the comprehensive scope of primary care — including what skills are necessary to care for patients from the beginning to the end of life — and advocated for the importance of disease prevention and health maintenance. Reports from the National Commission on Community Health Services (the so-called Folsom Report), the Citizens Commission on Graduate Medical Education (or Millis Report), and the Ad Hoc Committee on Education for Family Practice of the Council on Medical Education (known as the Willard Report), helped

many conclude that all graduates from medical school needed specialized training, including the "primary physician."[14]

Government payment systems also helped the U.S. education system expand physician and non-physician medical manpower. By 1969, when nearly all medical school graduates were choosing a specialty, Family Medicine became America's 20th primary specialty. Lancaster County's own Edward Kowalewski, MD, of Akron, was president-elect of the American Academy of Family Physicians and played a leading role in the implementation of the specialty. Medical school graduates soon tripled, and new health practitioner roles — including nurse practitioners, physician assistants, and nurse midwives — were developed to help meet the spectacular demand for health care. Currently, the American Board of Medical Specialties recognizes 40 specialties and 89 subspecialties.[15]

Lancaster-born John Herr Musser, MD, a professor at the University of Pennsylvania, served as president of the AMA from 1904-1905.

As of 2015, primary care physicians made up a third of the total workforce, with only 7% being pediatricians and 13% being internists; the remaining 13% were family physicians.[16] By 2024, the percentage of U.S. physicians practicing primary care had continued to drop, to less than a quarter of those who practice medicine.[17] The 2024 U.S. Health Resources and Services Administration State of the Primary Care Workforce report suggests that by 2037 there will be a shortfall of over 87,000 primary care physicians.[18]

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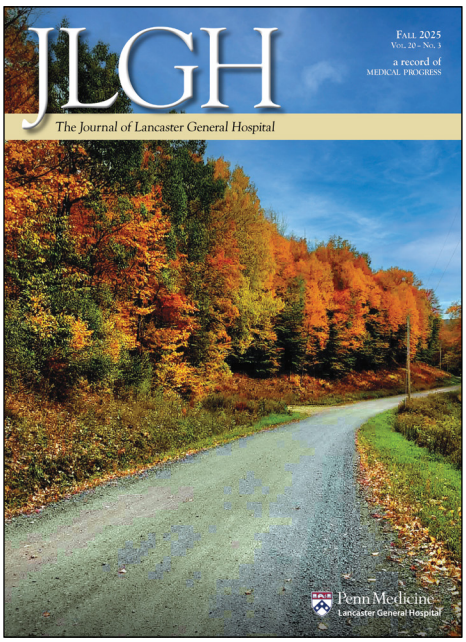

Cover photo by Gary Flory, husband of Barbara Flory, MHA, C-TAGME, director of graduate medical education and DIO (designated institutional official) at Penn Medicine Lancaster General Health. The photo showcases the Commonwealth's vibrant fall foliage on Paul Hollow Road on the outskirts of Galeton, Potter County.

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