Q2 2025 EDITION

Value Added

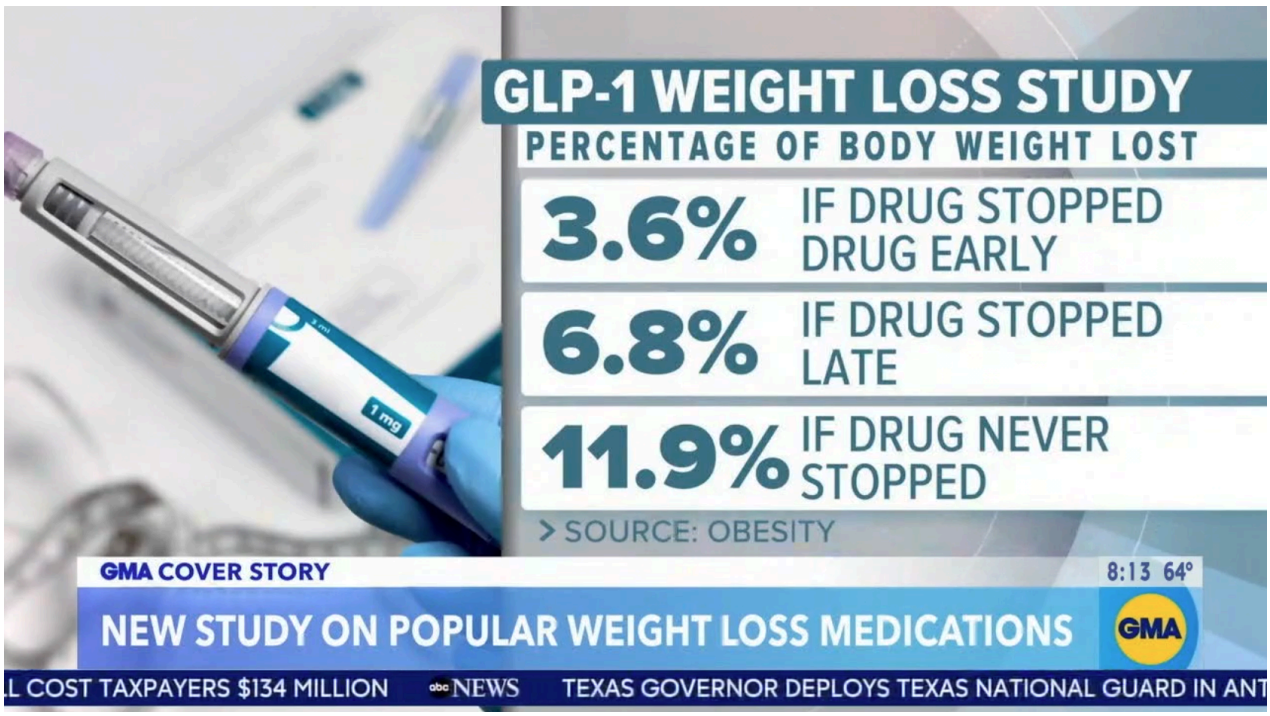
STAY IN THE LOOP WITH PUBLICATIONS AND UPDATES

AT A GLANCE

CVCR in the News

"Changes in weight and glycemic control following obesity treatment with semaglutide or tirzepatide by discontinuation status"

...was reported on by GMA, WEWS, US News, The Independent (redistributed by **Yahoo News** and **MSN**), and more.



GMA coverage of the study

Featured Publication - *C.diff*

Impact of empiric antibiotics on risk of *Clostridioides difficile* – a causal interference observational analysis

Q: Can you provide a lay summary of the article?

Dr. Pappas: One of the most feared complications of antibiotics is an infection called *Clostridioides difficile,* or *C.diff,* which is an infection of the colon, which occurs when antibiotics clear out lots of normal bacteria that live in the intestines and, in their place, a difficult to kill bacterium flourishes. And so, one of the things that we get concerned about when we give antibiotics for long periods of time or very potent antibiotics is that we will cause *C.diff,* and it can be a terrible complication.

The antibiotics that we give are clearly associated with *C.diff.* We know that the more antibiotics we give, the more cases of *C.diff* we find, but that association is highly confounded, and it's not clear how many of those cases of *C.diff* are because we extended antibiotics for too long or used overly broad antibiotics.

We know that patients with severe infection benefit from early aggressive antibiotic therapy. When we don't know what's causing the infection, we should, generally, treat for a wide variety of bacteria and then narrow our therapy... as we get more information. So, it would be really nice if we knew how much harm our antibiotics caused and not how much harm they were associated with. And so, my coauthors and I tried to estimate that harm by doing a few things.

So, first, we used a cohort of patients who were admitted with COVID in the first wave of the pandemic, so before widespread vaccine availability. The advantage of doing that is that all of the patients in this study were admitted with a viral infection, so there shouldn't really be relationships between use of an antibiotic and future outcomes. We often use broad spectrum antibiotics when people are very sick, but because, in this cohort, we know they were admitted with COVID, and we know COVID is not affected by bacteria, there's not a lot of reason to believe that the future outcomes are affected by one antibiotic or another, other than because of the antibiotic.

So, second, we used a causal inference observational design, which emulates a hypothetical trial where we would have taken patients where it wasn't clear whether to give an antibiotic or not and then randomized them to one of those two conditions. The ideal way to study this would be to take a large number of patients where you weren't sure if you should extend treatment by one day or stop it immediately and flipped a coin, and then, for half of them, gave an extra day of antibiotics, and for half of them, didn't, and then studied the outcomes. And although we will not have that randomized trial done prospectively, if you have a large number of patients and you know what things lead people to either extend or not extend antibiotics, you can emulate that. And so, I think because it's so hard and expensive to run a randomized trial where you did that in advance, this should be about the best evidence we have for how many cases of *C.diff* an extra day of antibiotics is likely to create.

Q: How did you end up using COVID patients?

In the first wave of the pandemic, HCA, the large for-profit healthcare corporation, which runs a lot of hospitals in the US, wanted to make some of its data available to researchers to study COVID, and the deputy director of AHRQ asked some hospitalist researchers around the country if there was something we might be able to do with that data set. But the thing that struck me about COVID was that everyone else in the country was studying COVID, and I couldn't think of a way in which I would contribute to care of COVID patients more than the recovery trial or the REMDESIVIR trial, which were large and industry funded. I couldn't think of a good way that, without a team, and grant money, and a big project already underway, I would be able to help take care of COVID patients immediately. But in thinking about how one could learn about how to better care for our patients while using a large data set with COVID, I started to think about the complications that we caused in caring for those patients.
And one of my old friends, Valerie Vaughn, had recently published a study showing that about half of patients hospitalized with COVID got antibiotics, which struck me as probably unhelpful since, again, it's a virus. And the 50% number stood out to me, and I thought, if it is true that about half of these patients are getting antibiotics that they don't need, and the antibiotics shouldn't affect future outcomes except through the complications that they cause, that would be an ideal group of patients in which to study this particular harm of antibiotics.

Q: How do you think that this study relates to the problematic overuse of antibiotics and the rise of antibiotic-resistant pathogens?

Dr. Pappas: Antibiotic resistance is important, both for patients themselves and for all of society. One interesting thing about antibiotics is that there are patient level harms: diarrhea, *C.diff*, allergic reactions, and there are complications like antimicrobial resistance that also have effects on everyone else in society. And so, antibiotics are, in some ways, a harder question of decision making because an ideal physician would balance both the responsibilities to his or her patient and try and make an optimal decision for his or her patient but also try to be a good steward of societal harms and societal resources. And I think this paper estimates *one* of the downstream harms of broad-spectrum antibiotics, just *C.diff*.
I hope that this approach that I took, of trying to rigorously estimate that harm of a therapy for which we don't have a randomized trial instead of just taking the associations at face value, can help us be smarter about lots of treatments that we use in the hospital.

I think it is very hard for humans to give appropriate weight to harms that are further into the future or only indirectly related to our actions. So, here, you might say "Selection for resistant organisms is a future problem and is only modestly related to whether I continue antibiotics today."
"C.diff is a future problem, one that's only a little bit related to whether I continue antibiotics today." I think it's hard for humans to give appropriate weight to those harms. I could invoke climate change for a broader example, right? What I do, what flight I take today, is only related to future climate change a little bit.
It's hard for us to give appropriate weight to those things, and so I would guess that most of us in medicine probably underestimate the harms of antibiotics only because human psychology makes it very hard for us to appropriately weight those future consequences. But that is a guess, not a carefully calculated estimate.

Q: What are optimal next steps for this study? Do you foresee future studies or interventional changes in practitioners?

Dr. Pappas: I think the most surprising thing from the results here were that this analysis suggests that IV vancomycin is perhaps the antibiotic that most increases risk of hospital-onset *C.difficile*. I do not know why that should be. I hope that smarter microbiologists can pick up that thread from here to try and better understand why that should be the case.
And, until we better understand that, because I think this is the best estimate of how much *C.diff* risk increases with a dose of antibiotics, I think a pathway for antimicrobial stewardship would be to be more careful about vancomycin than other antibiotics.

From my study, it seems like the difference between other broad-spectrum antibiotics and one another is fairly modest. The difference between Zosyn and levofloxacin, say, is pretty modest. The difference between Zosyn and ceftriaxone is fairly modest, but the difference between vancomycin and no vancomycin is bigger. And so, if you were trying to be more mindful of how frequently you were exposing patients to unnecessary antibiotics, vancomycin would be a good one to try and focus on. In part because we only add it for one organism, for MRSA. Most of the broad-spectrum antibiotics, like Zosyn, that we use cover resistant forms of Staph aureus, as well as other organisms. We add vancomycin because MRSA isn't. And because vancomycin seems to be the organism that most precipitates *C.diff*, and we can test for MRSA, it should be the one that we can deescalate most quickly. And so, I think that is a promising target for how to take better care of patients in the interim, even as I hope our microbiologists will think more carefully about why that should be in the first place, which, as I said, I don't think I understand.

Featured Publication - MASLD

Association of Components of Metabolic Syndrome and the Progression of Nonalcoholic Fatty Liver Disease

Q: Can you provide a lay summary of the study?

A: This study aimed to understand how metabolic syndrome (MetS) and its individual components affect the progression or improvement of nonalcoholic fatty liver disease (NAFLD). NAFLD is a condition where fat builds up in the liver without alcohol being involved and can lead to liver damage over time. The condition is recently changed to call metabolic dysfunction associated steatotic liver disease. In our study, metabolic syndrome was defined as having 3 or more metabolic risk factors including large waist circumference, high blood sugar, high blood pressure, low HDL cholesterol, and high triglyceride.

Using data from a large, long-term study involving 452 adults with confirmed NAFLD and an average follow up of 4.3 years, we found that while metabolic syndrome was linked to more severe liver damage at the beginning of the study, it didn't appear to be a key factor in whether the disease got worse or better over time. However, patients with high blood sugar or diabetes had a higher risk of fibrosis progression, while those with high blood pressure were less likely to experience worsening.

Q: How did this study come about? Is this a follow up study from previous research?

A: Previous research showed the associations between metabolic syndrome and severity of NAFLD, but none has looked at the effect of metabolic syndrome on disease progression. This study builds on previous research by exploring new aspects of how metabolic syndrome interacts with NAFLD over time, and it uses data from the ongoing NASH CRN registry, which has allowed us to track these effects in detail.

Q: Were there any results you weren't expecting/were surprised by?

A: Yes, there were a couple of surprising findings. One of the most unexpected results was that metabolic syndrome itself was not associated with fibrosis progression or regression, even though it was linked to more severe liver disease at baseline. We often think of metabolic syndrome as a key driver of NAFLD outcomes, so we expected it to be predictive of disease trajectory over time. One reason for this could be that MetS is a broad, composite diagnosis. It may "dilute" the effects of the individual risk factors. For example, in our study, impaired glucose tolerance or diabetes was clearly associated with fibrosis progression, but other components were not. So, if you bundle them all together, you might miss the signals from the individual components that actually matter most.

Another surprising result was that hypertension was associated with a lower risk of fibrosis progression. That's counterintuitive, since hypertension is typically viewed as a harmful factor in metabolic diseases. One hypothesis is that certain antihypertensive medications—like ACE inhibitors or ARBs—may have protective effects on the liver, but our study wasn't designed to test that directly. The data also did not have information about these specific medications.

This finding definitely warrants further investigation.

Q: Why is research in this area important to continue?

A: Research in this area is critically important because nonalcoholic fatty liver disease (NAFLD) is now one of the most common chronic liver conditions worldwide, and it can progress to serious outcomes like cirrhosis, liver failure, and even liver cancer. Yet, we still don't fully understand which patients are most at risk of progression and how to best intervene early.

Our findings highlight that not all metabolic risk factors contribute equally to disease progression, which means that lumping them together under the umbrella of metabolic syndrome may not be the most effective approach. Continuing research can help refine risk prediction, identify which patients need the most aggressive management, and ultimately lead to more personalized and targeted treatment strategies.

In the long term, better understanding of the mechanisms linking metabolic health and liver disease could also open the door to new therapies and prevention strategies—not just for liver disease, but for the broader metabolic diseases that often accompany it.

Q: What are optimal next steps for this study? Do you foresee future studies or interventional changes on the physician level?

A: The next logical step is to validate these findings in larger and more diverse populations, especially since our cohort was predominantly White and came from specialized liver centers. We also need to explore the underlying mechanisms behind why some individual components of metabolic syndrome – like impaired glucose tolerance – drive fibrosis progression while others, like hypertension, may not – or might even be protective. These insights could help clinicians move beyond viewing metabolic syndrome as a single risk category and instead focus on individual risk factors when assessing and managing NAFLD.

From an interventional standpoint, our findings support a more targeted approach—particularly for patients with diabetes or prediabetes, who may be at highest risk for fibrosis progression. This is especially relevant now, given the emergence of new medications like GLP-1 receptor agonists (e.g. semaglutide) and dual agonists (e.g., tirzepatide), which show promise in improving both metabolic health and liver outcomes.

Incorporating these treatments into liver care—especially for patients with coexisting metabolic risk factors—could be a game-changer. But we still need more research to determine which patients benefit most, how early to intervene, and whether these therapies actually prevent or reverse fibrosis in the long term.

Celebrations

Congratulations to all of our staff and students on their promotions and awards from this past quarter!

Dr. Hamlet Gasoyan received the 2025 Rolls-Simon Travel Award for his abstract "*Reasons for Discontinuation of Semaglutide or Tirzepatide for Obesity in Clinical Practice.*"

Dr. Christopher Boyer was officially appointed as Assistant Professor of Medicine at CWRU.

August Culbert, a student of Dr. Abhishek Deshpande, was selected as one of the 2025 Internal Medicine and Geriatrics Arthur S and Arlene M Holden Scholars Award winners. This came with an invitation to present at SGIM, a national conference.

Dr. Elizabeth Pfoh was officially promoted and approved to begin using her new title of Associate Professor at CCLCM.

Recent Publications

Abu Omar Y, Sullivan E, Schulte R, Pichardo R, Rothberg MB. **White Blood Counts of Hospitalized Patients Without Infection, Malignancy, or Immune Dysfunction**. South Med J. 2025 May;118(5):287-292. doi: 10.14423/SMJ.0000000000001820. PMID: 40316273.

Adekunle OA, Le P, Gupta DY, Rothberg MB, Tran HT, Yue Y, Gasoyan H. **Socio-demographic and clinical factors associated with the receipt of anti-obesity medication prescriptions and metabolic and bariatric surgery among eligible all of Us participants**. Diabetes Obes Metab. 2025 Jun 19. doi: 10.1111/dom.16544. Epub ahead of print. PMID: 40537972.

Floden DP, Hogue O, Saxena SA, Misra-Hebert AD, Milinovich A, Rothberg MB, Pfoh ER, Busch RM, Krishnan K, Fox RJ, Kattan MW. **Automated identification of older adults at risk for cognitive decline**. Alzheimers Dement (Amst). 2025 Jun 12;17(2):e70136. doi: 10.1002/dad2.70136. PMID: 40520422; PMCID: PMC12162263.

Gasoyan H, Butsch WS, Schulte R, Casacchia NJ, Le P, Boyer CB, Griebeler ML, Burguera B, Rothberg MB. **Changes in weight and glycemic control following obesity treatment with semaglutide or tirzepatide by discontinuation status**. Obesity (Silver Spring). 2025 Jun 10. doi: 10.1002/oby.24331. Epub ahead of print. PMID: 40491239.

Gunaratne T, Schulte R, Moss S, Lisheba O, Rothberg MB. **Use of a Risk Assessment Model for Venous Thromboembolism Is Associated with Decreased Prophylaxis**. J Gen Intern Med. 2025 May 8. doi: 10.1007/s11606-025-09592-6. Epub ahead of print. PMID: 40341484.

Le P, Dasarathy S, Herman WH, Adekunle OA, Tran HT, Criswell V, Ye W, Welch N, Yue Y, Rothberg MB. **Value-Based Pricing of Resmetirom for Metabolic Dysfunction-Associated Steatotic Liver Disease**. JAMA Netw Open. 2025 Jun 2;8(6):e2517122. doi: 10.1001/jamanetworkopen.2025.17122. PMID: 40577015; PMCID: PMC12205400.

Le P, Kaya E, Phan A, Yilmaz Y, Alkhouri N. **Resmetirom-eligible population among US adults: An estimation analysis based on NHANES 2017-March 2020**. Hepatol Commun. 2025 Jun 19;9(7):e0755. doi: 10.1097/HC9.0000000000000755. PMID: 40536500; PMCID: PMC12180822.

Martinez KA, Montori VM, Rodriguez F, Tereshchenko LG, Kovach JD, Boyer C, Hurwitz HM, Rothberg MB. **Association between Exposure to Statin Choice and Adherence to Statins: An Observational Cohort Study**. Med Decis Making. 2025 Jun 24:272989X251346508. doi: 10.1177/0272989X251346508. Epub ahead of print. PMID: 40553465.

Mehta S, Haddad EN, Burke IB, Majors AK, Maeda R, Burke SM, Deshpande A, Nowacki AS, Lindenmeyer CC, Mehta N. **Assessment of Large Language Model Performance on Medical School Essay-Style Concept Appraisal Questions: Exploratory Study**. JMIR Med Educ. 2025 Jun 16;11:e72034. doi: 10.2196/72034. PMID: 40523238.

Mittman BG, Rothberg MB. **Estimated Impact of Model-Guided Venous Thromboembolism Prophylaxis versus Physician Practice**. medRxiv [Preprint]. 2025 May 31:2025.05.29.25328593. doi: 10.1101/2025.05.29.25328593. PMID: 40492076; PMCID: PMC12148274.

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