Things We Do For No Reason™: Routinely Holding Metformin in the Hospital

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Inspired by the ABIM Foundation's *Choosing Wisely*® campaign, the "Things We Do for No Reason™" (TWDFNR) series reviews practices that have become common parts of hospital care but may provide little value to our patients. Practices reviewed in the TWDFNR series do not represent clear-cut conclusions or clinical practice standards but are meant as a starting place for research and active discussions among hospitalists and patients. We invite you to be part of that discussion.

CLINICAL SCENARIO

A hospitalist admits a 29-year-old man with hypertension, obesity, and type 2 diabetes (type 2 DM) for a posterior neck abscess that failed outpatient oral antibiotic therapy. The patient's medications include metformin monotherapy. Vital signs taken upon admission include a blood pressure of 136/82 mm Hg, heart rate of 98 beats per minute, respiratory rate 18 of breaths per minute, oxygen saturation of 100% on room air, and temperature of 38.5 °C. Laboratory evaluation revealed a glucose level of 212 mg/dL, with a hemoglobin A1c of 8.0%, lactic acid of 1.4 mmol/L, and normal renal and hepatic function. Based on these findings, the hospitalist holds metformin and starts the patient on sliding-scale insulin therapy.

WHY YOU MIGHT THINK ROUTINELY HOLDING METFORMIN IN THE HOSPITAL IS NECESSARY

Metformin, an oral medication used to treat type 2 DM, is a biguanide that increases peripheral glucose utilization and decreases hepatic gluconeogenesis. However, metformin-associated shunting of metabolism toward anaerobic respiration increases the risk of lactic acidosis.[1] Because the kidneys excrete metformin, the risk of developing metformin-associated lactic acidosis (MALA) increases with renal impairment. Disease states common among hospitalized patients, such as hypoperfusion, advanced cirrhosis, alcohol abuse, cardiac failure, muscle ischemia, and severe infection, increase the risk of acute kidney injury (AKI) and elevate blood lactate levels. Therefore, hospitalists regularly hold metformin in the inpatient setting.

Following the introduction of metformin in the United States, the US Food and Drug Administration (FDA) received 47 confirmed reports of nonfatal lactic acidosis associated with the use of metformin, all of which involved cardiac disease (specifically congestive heart failure [CHF]), renal insufficiency, hypoxia, or sepsis.[2] Consequently, the FDA listed CHF as a contraindication to metformin use; however, it has since changed the use of metformin in CHF from a contraindication to a warning/precaution for lactic acidosis. The FDA also added a warning against the use of metformin in patients with sepsis or in patients older than 80 years who have abnormal creatinine clearance.

Acute kidney injury, a common inpatient condition, occurs in 20% of hospitalized patients and more than 50% of intensive care patients.[3] Moreover, a retrospective observational study showed approximately 50% of all patients hospitalized for COVID-19 had AKI.[4] Iodinated contrast, a diagnostic media commonly used in the hospital, may also increase the risk of renal dysfunction. The FDA recommends providers discontinue metformin at or before initiating imaging studies with iodinated contrast[5] in patients with an estimated glomerular filtration rate (eGFR) between 30 and 60 mL/min/1.73 m^2. The FDA also advises that providers not restart metformin until 48 hours after an intra-arterial (IA) or intravenous (IV) contrast study in patients with an eGFR <60 mL/min/1.73 m^2 (equivalent to chronic kidney disease [CKD] stage 3 or worse).[5] The American Diabetes Association (ADA) recommends the same eGFR cutoff level in its clinical practice recommendations, as well as withholding metformin 48 hours before patients receive IV contrast.[6] Given the risk of AKI in hospitalized patients and concerns of increased MALA, clinicians reflexively hold metformin.

Holding metformin is also consistent with professional guidelines. The 2009 American Association of Clinical Endocrinology and ADA Consensus Statement on Inpatient Glycemic Control recommends cautious use of metformin in the inpatient setting "because of the potential development of a contraindication during the hospitalization."[7] Similarly, the 2012 Endocrine Society guidelines recommend withholding metformin in almost all hospitalized patients.[8]

WHY ROUTINELY HOLDING METFORMIN IN THE HOSPITAL IS NOT BENEFICIAL

Routinely holding metformin in hospitalized patients is unnecessary and potentially harmful. First, MALA is exceedingly rare, and experts question the causal link. Furthermore, iodinated contrast does not place patients with normal renal function at increased risk of MALA. Finally, holding metformin leads to worsened glycemic control and increased use of insulin, both of which may result in adverse patient outcomes.

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Received: August 17, 2020; **Revised:** April 26, 2021; **Accepted:** April 27, 2021

 DOI 10.12788/jhm.3644

TABLE. **Summary of Studies Indicating Metformin Does Not Cause Lactic Acidosis in the Absence of Other Risk Factors**

Source	Study design	Population	Setting	Methods, duration	Brief summary
Brown et al,[12] 1998	Retrospective chart review	41,426 person-years	Outpatient and inpatient	Registry review of hospital discharges and laboratory results from Kaiser Permanente across three regions	Lactic acidosis occurs in metformin users at a rate of 9.7/100,000 person-years of exposure, similar to all persons with diabetes.
Lalau et al,[13] 1999	Cross-sectional study	49 patients	Inpatient	Lactate levels and metformin concentration were obtained from hospitalized patients with lactic acidosis during metformin therapy and analyzed for correlation and association with mortality	Accumulation of metformin does not correlate with lactate levels or have any prognostic significance.
Salpeter et al,[14] 2010	Systematic review	70,940 patient-years of metformin use	Outpatient and inpatient	Pooled data from 347 prospective trials and observational cohort studies	Incidence of lactic acidosis per 100,000 patient-years was 4.3 cases in the metformin group and 5.4 cases in the nonmetformin group.
Ekström et al,[10] 2012	Cohort study	51,675 patients	Outpatient	Population-based longitudinal study linked from four national registers in Sweden	Metformin showed reduced risks of acidosis/severe infection and all-cause mortality in patients with eGFR 45-60 mL/min/1.73 m^2, and no increased risks of acidosis/severe infection or all-cause mortality in patients with eGFR 30-45 mL/min/1.73 m^2.
Lalau et al,[11] 2018	Experimental	83 patients	Outpatient	Patients with type 2 diabetes and CKD given variable doses of metformin over 4 months to determine metformin and lactate concentrations	For stable patients on doses of metformin adjusted for renal function, there was no increase in lactate levels.
Lazarus et al,[15] 2018	Cohort study	75,143 patients	Outpatient	Community-based patients with type 2 diabetes and creatinine measurements; data obtained from problem lists, prescriptions, diagnostic codes, and laboratory measurements	Patients on metformin with eGFR >30 mL/min/1.73 m^2 had no increase in hospital admission with acidosis, though there was an increased risk with eGFR <30 mL/min/1.73 m^2.

Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

The concerns about MALA stem from clinical experiences with phenformin, an older and more potent biguanide. Phenformin shares a similar mechanism of action with metformin but causes more lactic acid production. In 1978, following 306 documented cases of phenformin-associated lactic acidosis, the FDA removed this medication from the market.[9] Since the initial 47 cases of MALA were reported to the FDA, repeated studies and systematic reviews have disputed the link between metformin and lactic acidosis, particularly in the absence of significant risk factors or in patients with an eGFR ≥30 mL/min/1.73 m^2. In fact, a large observational study showed a reduction in acidosis and mortality in outpatients with stage 3a CKD (eGFR, 45-59 mL/min/1.73 m^2) who were taking metformin compared to patients taking insulin or other oral hypoglycemics agents.[10] In patients with stage 3b CKD (eGFR, 30-44 mL/min/1.73 m^2), this study found no difference in the same outcomes.[10]

Studies show that metformin does not cause elevated lactate levels in patients with stage 4 CKD (eGFR >15mL/min/1.73^2) or lower stages of CKD as long as doses are adjusted appropriately to reflect renal function.[11] These and other investigations reveal that in the absence of other risk factors, metformin does not cause lactic acidosis (Table).[10-15] Based on these findings, the Endocrine Society changed the strength of its recommendation to withhold metformin in hospitalized patients to "weak," with "very low-quality evidence." The FDA similarly revised its warnings[8] to allow metformin use in all patients with an eGFR ≥30 mL/min/1.73 m^2. A large community-based cohort study, which demonstrated no association between hospitalization with acidosis and metformin use in patients with stage 3b CKD or lower stages of CKD, supports this change in treatment threshold.[15]

Published evidence also does not support the practice of routinely holding metformin before contrast administration, despite concerns regarding contrast-induced nephropathy. Retrospective chart reviews and a direct comparison in human models have not shown any significant difference in the risk of AKI between the IV and IA contrast.[16] Moreover, evidence suggests no interaction between metformin and contrast media in patients with normal renal function.[17] In response, the American College of Radiology, Canadian Association of Radiology, Royal College of Radiologists, and Royal Australian and New Zealand College of Radiologists all recommend continuing metformin in patients with normal renal function (eGFR ≥30 mL/min/1.73m^2) receiving IV contrast. They advise holding metformin for 48 hours in patients with renal insufficiency (eGFR <30 mL/min/1.73m^2) or those undergoing IA catheter studies that might result in renal artery emboli.[18]

Finally, continuing metformin maintains steady blood glucose control. The practice of replacing metformin with sliding-scale insulin monotherapy for hospitalized patients significantly increases the risk of hyperglycemia and is associated with an increased length of stay.[19] Additionally, unlike

insulin, metformin does not increase the risk of hypoglycemia. Finally, a recent matched cohort study comparing the use of oral hypoglycemic agents (metformin, thiazolidines, and sulfonylureas) vs insulin monotherapy in patients undergoing emergency abdominal surgery showed that the patients admitted with sepsis and treated with oral agents had a lower 30-day mortality rate and a shorter length of stay.[20] Based on the evidence showing that inpatient oral hypoglycemic agents improve quality metrics and mitigate safety events, the ADA advocates resuming oral antihyperglycemic medications (most commonly metformin) 1 to 2 days before discharge.[7]

WHAT YOU SHOULD DO INSTEAD

Clinicians should continue metformin in all hospitalized patients who are not at significant risk of developing lactic acidosis. Risk factors for MALA include severe sepsis (in the setting of end-organ damage as defined by systemic inflammatory response syndrome criteria), hypoxia requiring oxygen supplementation, hypoperfusion (as from CHF), AKI, CKD (eGFR <30 mL/min/1.73 m^2), and advanced cirrhosis. Given the high rates of hypoxia and AKI in admitted patients with COVID-19, clinicians should hold metformin on admission. Continue metformin for patients receiving IV contrast media with an eGFR >30 mL/min/1.73 m^2. For patients undergoing IA catheter studies associated with a risk for renal artery emboli, or in patients with renal insufficiency (eGFR <30 mL/min/1.73 m^2), temporarily hold metformin for 48 hours. When held, restart metformin as soon as risk factors resolve.

RECOMMENDATIONS

- Hold metformin in patients with or undergoing the following:
  - High risk for or currently suffering from decompensated heart failure, severe sepsis, or other disease states resulting in hypoxia or tissue hypoperfusion;
  - An eGFR <30 mL/min/1.73 m^2 or AKI; resume metformin when the AKI resolves;
  - COVID-19 infection, until the risk of hypoxia has resolved;
  - IV contrast study in the presence of acute renal failure or an eGFR <30 mL/min/1.73 m^2; resume metformin 48 hours after contrast administration;
  - Intra-arterial catheter study that might result in renal artery emboli; resume metformin when renal function normalizes.
- Continue metformin in all hospitalized patients in the absence of the aforementioned disease states or contrast-related indications.

CONCLUSION

Returning to the patient in our clinical scenario, we recommend continuing metformin given the lack of risk factors or disease states associated with increased lactic acidosis. The practice of withholding metformin in hospitalized patients for fear of MALA is based on minimal evidence. Clinicians should, however, hold metformin in patients who have true contraindications, including existing acidosis, hypoperfusion, renal insufficiency, CHF, severe sepsis, hypoxia, advanced cirrhosis, and COVID-19. With regard to iodinated contrast studies, temporarily withhold metformin for 48 hours in patients with an eGFR <30 mL/min/1.73 m^2, acute kidney injury, or in patients undergoing an IA catheter study at risk for renal artery emboli. Patients should be restarted on metformin 48 hours after these studies and as renal function normalizes. When withholding metformin during a hospitalization, restart it once risk factors have resolved.

Do you think this is a low-value practice? Is this truly a "Thing We Do for No Reason™"? Share what you do in your practice and join in the conversation online by retweeting it on Twitter (#TWDFNR) and liking it on Facebook. We invite you to propose ideas for other "Things We Do for No Reason™" topics by emailing TWDFNR@hospitalmedicine.org

Disclosures: The authors have no conflicts to disclose.

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