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Original Research

Administration of a Methylprednisolone Taper and Complication Rates Following Total Knee Arthroplasty: A Multicenter Retrospective Study

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ABSTRACT

Background: Most patients undergoing total knee arthroplasty (TKA) report moderate to severe pain in the acute postoperative period. Recent preliminary data have suggested that a short course of oral corticosteroid may improve early postoperative pain after various orthopedic operations, but the safety of this practice has not been rigorously evaluated in larger patient populations. The purpose of this study was to evaluate complication rates in patients receiving a methylprednisolone taper (MT) vs controls after primary TKA.

Methods: Records were reviewed for patients undergoing primary TKA from 2018 to 2023 by 2 surgeons at different institutions who began routinely prescribing a 6-day MT to patients without a contraindication or poorly controlled diabetes. The primary outcome of periprosthetic joint infection at 90 days and final follow-up was assessed as were secondary outcomes of surgical site infection and wound complications. A total of 930 patients were included in the study, with 641 patients in the control cohort and 289 patients in the methylprednisolone cohort.

Results: There were no significant differences between the methylprednisolone and control cohorts in 90-day periprosthetic joint infection (0.7% vs 0%, $P = .1$, respectively), surgical site infection (1.0% vs 1.4%, $P = .4$, respectively), or wound complication (1.0% vs 2.0%, $P = .4$, respectively). There were no significant differences in any complication at final follow-up.

Conclusions: MT following TKA did not significantly increase rates of wound complications or infections in this multi-institutional retrospective cohort study. This study provides preliminary evidence regarding the safety profile of a short duration of postoperative oral corticosteroids following TKA.

Introduction

Postoperative pain is a critical issue for patients undergoing total knee arthroplasty (TKA) with 60% of patients reporting severe pain and another 30% reporting moderate pain after surgery [1]. Poorly controlled pain in the early postoperative period has been shown to be associated with decreased ambulation, impaired recovery, and poorer long-term functional outcomes [2,3]. Opioids remain commonly prescribed to manage severe pain following total joint arthroplasty [4,5]. While opioids are potent analgesics, they are associated with multiple, well-documented risks [2,4-8]. Consequently, there is a concerted effort to reduce the quantity of opioids prescribed after surgery through the use of multimodal analgesic strategies [2,5,6,9].

One class of medications with promising analgesic potential is corticosteroids [9]. Perioperative intravenously administered corticosteroids have been shown to decrease perioperative pain, nausea, and vomiting while reducing length of stay after total joint arthroplasty [2,3,7,10,11]. These effects may be related to a reduction in postoperative acute phase response [12]. Additionally, some evidence suggests opioid consumption may be decreased

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after TKA when intravenous (IV) corticosteroids are used [3,9,13,14].

Short-term corticosteroids, often given as an oral taper, are widely prescribed for indications such as sports injuries, upper respiratory tract infection, spinal pathology, and osteoarthritis [15-18]. Although some common side effects include hyperglycemia, hypertension (HTN), and sleep disturbances, short courses of corticosteroids are well tolerated, and major events such as sepsis, venous thromboembolism (VTE), and osteonecrosis occur rarely [19,20]. Due to its wide availability, low cost, favorable pharmacokinetics, and ease of use, oral methylprednisolone taper (MT) is an excellent option for use for short-term postoperative analgesia [21-24].

In light of the reported benefits of perioperative IV corticosteroids, there is growing interest in the addition of short-term oral corticosteroids following joint arthroplasty to alleviate pain and nausea. While chronic oral steroid use has been associated with an increased risk of perioperative complications such as superficial and deep infection, wound dehiscence, and readmission following total joint arthroplasty, perioperative IV administration has not been shown to carry these risks [3,9,25]. Limited data exist on the safety of short-term oral corticosteroids following total joint replacement. The present study aims to evaluate complications after administration of a standard oral MT in the acute postoperative period after TKA.

Material and methods

Data source and patient selection

Following institutional board review approval, electronic medical records were queried for patients undergoing TKA from January 1, 2018 to June 30, 2023 by 2 surgeons (J. R. and G. P.) at 2 separate institutions. Both surgeons independently began prescribing MTs following TKA during this 5-year period at academic hospitals. Both surgeon 1 (J. R.) (2019) and surgeon 2 (G. P.) (2022) began routinely prescribing MT to patients; however, patients with diabetes or a clear contraindication (eg, allergy) were generally excluded from receiving MT except for patients with well-controlled diabetes and mild disease severity. Both surgeons prescribed a single dose of IV steroids at time of surgery; however, surgeon 2 did not administer IV steroids to patients with diabetes. Only patients who underwent primary TKA with a diagnosis of primary osteoarthritis were included. Patients with prior joint infection, active infection at time of index procedure, and duplicate records were excluded from the study as were patients with less than 90 days of follow-up postoperatively. Patient records were examined to identify whether they received an MT following surgery. The MT is a standard prescription that consists of a pack containing a 6-day taper of oral methylprednisolone from a dose of 24 mg and decreasing by 4 mg each day till the final day. Patients receiving the MT began on postoperative day 1. A total of 1286 records were reviewed from both participating institutions. After applying exclusion criteria, a total of 931 patients were included in the study, with 641 patients in the control cohort and 290 patients in the methylprednisolone cohort. There were 699 patients from one institution (surgeon 1) and 232 patients from the other (surgeon 2) included in the study. The 355 additional records obtained during initial data collection were excluded based on a lack of 90-day follow-up (300, 84.5%), duplicated records (50, 14.1%), and patients with prior or active joint infection (5, 1.4%).

Baseline patient data and comorbidities

The following baseline patient data and comorbidities were collected during review of patient records: age, sex, preoperative knee range of motion (flexion and extension), presence of HTN, coronary artery disease, congestive heart failure, chronic kidney disease, rheumatoid arthritis, atrial fibrillation, chronic obstructive pulmonary disease, diabetes mellitus (DM), hypothyroidism, anticoagulation use, hyperlipidemia, smoking status, obesity, gastroesophageal reflux disease, prior VTE, any autoimmune disease, prior malignancy, anxiety, and depression. Comorbidities were assigned based on presence of at least 1 physician-labeled diagnosis in the patients' records. Patients with active diabetes were identified based on a prior diagnosis and an available preoperative hemoglobin A1C above 6.5 mg/dL. There was no significant difference in patient age or preoperative range of motion between cohorts. However, patients receiving an MT were more likely to be female (88% vs 83%, $P = .038$), undergo spinal anesthesia (95% vs 92%, $P = .038$), and receive a cruciate retaining implant (81% vs 70%, $P = .004$) with cemented fixation (92% vs 87%, $P = .023$) (Table 1). Baseline patient comorbidities are listed in Table 2. There were significantly more patients who had depression in the methylprednisolone cohort (18% vs 12%, $P = .010$), while there were more patients who had HTN in the control cohort (20% vs 13%, $P = .018$). There were more diabetic patients in the control cohort (22% vs 12%, $P < .001$); however, preoperative A1C among diabetic patients was not significantly different between the 2 cohorts (6.4% vs 6.2%, $P = .12$). Otherwise, there were no other statistically significant baseline differences in comorbidities.

Table 1
Baseline patient and surgical characteristics.

Characteristic	No medrol, n = 641[a]	Medrol received, n = 290[a]	*P* value[b]
Age (y)	70 (10)	69 (10)	.6
Sex			**.038**
Female	529 (83)	254 (88)	
Male	112 (17)	35 (12)	
Anesthesia type			**.038**
General	48 (8.0)	12 (4.4)	
Spinal	573 (92)	260 (95)	
Combined	0 (0)	1 (0.6)	
Peripheral block agent			**.023**
Ropivacaine	269 (42.0)	135 (46.7)	
Lidocaine/ropivacaine	154 (24.0)	73 (25.3)	
Mepivacaine	148 (23.1)	48 (16.6)	
Bupivacaine	6 (0.9)	5 (1.7)	
Lidocaine	30 (4.7)	5 (1.7)	
Other	34 (5.3)	23 (8.0)	
Implant type			**.004**
CR	431 (70)	232 (81)	
PS	3 (0.6)	1 (0.3)	
TS	5 (0.6)	1 (0.3)	
UC	178 (29)	53 (18)	
Cemented fixation	557 (87)	266 (92)	**.023**
Preoperative extension			.8
0°-10°	590 (97.7)	262 (98.5)	
11°-20°	8 (1.3)	3 (1.1)	
>20°	6 (1.0)	1 (0.4)	
Preoperative flexion			.053
0°-90°	57 (9.1)	19 (7.0)	
90°-120°	310 (49.7)	117 (43.2)	
>120°	257 (41.2)	135 (49.8)	

CR, cruciate retaining; PS, posterior stabilizing; TS, total stabilizing; UC, ultra-congruent.
Bold values indicate statistical significance ($P < .05$).
[a] Mean (SD); n (%); n (%).
[b] Welch 2-sample *t*-test, Pearson's Chi-squared test, Fisher's exact test.

Table 2
Baseline patient comorbidities.

Characteristic	No medrol,[a] n = 641	Medrol received,[a] n = 290	*P* value[b]
ASA			.9
1	9 (1.4)	3 (1.0)	
2	286 (45)	123 (43)	
3	341 (53)	162 (56)	
4	4 (0.6)	1 (0.3)	
Smoker	30 (4.7)	7 (2.4)	.10
Obesity	316 (50)	145 (51)	.8
Diabetes	138 (22)	36 (12)	**<.001**
Preoperative A1C[c]	6.4 (0.91)	6.2 (1.02)	.12
Hypertension	125 (20)	38 (13)	**.018**
Chronic kidney disease	40 (6.2)	17 (5.9)	.8
Autoimmune disease	41 (6.4)	15 (5.2)	.5
Anxiety	73 (11)	41 (14)	.2
Depression	77 (12)	53 (18)	**.010**
COPD	10 (1.6)	7 (2.4)	.4
Hypothyroidism	78 (12)	32 (11)	.6
Atrial fibrillation	42 (6.6)	11 (3.8)	.095
GERD	138 (22)	77 (27)	.087
CAD	63 (9.8)	21 (7.3)	.2
CHF	13 (2.0)	6 (2.1)	>.9
HLD	222 (35)	117 (40)	.086
Prior VTE	85 (13)	47 (16)	.9
Prior malignancy	102 (16)	45 (16)	.9

ASA, American Society of Anesthesiologists; CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; HLD, hyperlipidemia; VTE, venous thromboembolism.
Bold values indicate statistical significance ($P < .05$).
[a] n (%).
[b] Welch 2-sample *t*-test; Pearson's Chi-squared test; Fisher's exact test.
[c] Mean (SD).

Table 3
Univariable analysis of outcomes after TKA.

Outcome	No medrol,[a] n = 641	Medrol received,[a] n = 290	*P* value[c]
90-day			
PJI	0 (0)	2 (0.7)	.1
SSI	9 (1.4)	3 (1.0)	.4
Wound complication	13 (2.0)	3 (1.0)	.4
Vascular injury	0 (0)	0 (0)	-
VTE	1 (0.2)	2 (0.7)	.2
MUA	9 (1.4)	4 (1.4)	>.9
Flexion contracture	10 (1.6)	0 (0)	**.036**
Readmission	25 (3.9)	9 (3.1)	.6
Postoperative extension			.2
0°-10°	631 (99.0)	290 (98.0)	-
11°-20°	7 (0.8)	7 (1.1)	-
>20°	3 (0.3)	3 (0.5)	-
Postoperative flexion			.12
0°-90°	73 (11.4)	20 (6.9)	-
90°-120°	523 (81.6)	24 (85.5)	-
>120°	45 (7.0)	22 (7.6)	-
Latest follow-up			
Follow-up length	431 (350)[b]	335 (323)[b]	**<.001**
PJI	1 (0.2)	2 (0.7)	.7
Mechanical complication	0 (0)	0 (0)	-
Instability	9 (1.4)	5 (1.7)	>.9
Implant loosening	0 (0)	0 (0)	-
Periprosthetic fracture	2 (0.3)	1 (0.3)	>.9
Any reoperation	8 (1.2)	3 (1.0)	>.9
Revision	2 (0.3)	3 (1.0)	.2

MUA, manipulation under anesthesia; PJI, periprosthetic joint infection; SSI, surgical site infection; TKA, total knee arthroplasty; VTE, venous thromboembolism.
Flexion contracture = Postoperative extension > 10°.
Bold values indicate statistical significance ($P < .05$).
[a] n (%).
[b] Mean (SD).
[c] Welch 2-sample *t*-test; Fisher's exact test; Pearson's Chi-squared test.

Surgical characteristics and operative technique

Data regarding surgical technique and characteristics were also obtained, which included information on prosthesis type used (eg, cruciate retaining, posterior stabilized, ultracongruent), mode of anesthesia (general vs spinal vs both), fixation method (cemented vs press-fit), and anesthetic agent used for peripheral nerve block. For all cases, a standard medial parapatellar arthrotomy was used. Aspirin 81 mg twice daily was used for deep vein thrombosis prophylaxis in the majority of patients from both institutions except in the presence of prior thromboembolic event or hypercoagulable state.

Complications and outcomes

The primary outcome of interest in this study was incidence of periprosthetic joint infection (PJI) at 90 days and at final follow-up. Other secondary outcomes were also included in our analysis. These were 90-day rates of superficial surgical site infection (SSI), wound complication, periprosthetic fracture, VTE, vascular injury, nerve injury, flexion contracture, postoperative flexion and extension, readmission, and manipulation under anesthesia. Rates of instability, implant loosening, mechanical complication, any revision, and any reoperation were assessed at latest follow-up. Wound complications were defined as wound dehiscence, delayed wound closure, or impaired healing, while SSIs were based on clinical concern for infection requiring a course of oral antibiotics. Flexion contracture was defined as a final postoperative extension measurement of less than 10° of full extension.

Data analyses

All statistical calculations were performed using R-Studio (RStudio Team, Boston, MA) [26]. Baseline patient characteristics, comorbidities, and surgical characteristics were analyzed using *Chi*-square tests for categorical variables and Welch 2-sample *t*-tests for quantitative variables. Similarly, *Chi*-square tests and Welch 2-sample *t*-tests were used to analyze rates of postoperative complications. Multivariable analysis could not be performed due to low event rates for all complications. Statistical significance was considered at $P < .05$.

Results

Univariate analysis of outcomes is listed in Table 3. Mean follow-up was significantly longer in the control cohort (431 vs 335 days, $P < .001$), as expected, as both surgeons transitioned to routinely prescribing methylprednisolone later in the study period. At 90 days, there were 2 cases of PJI, both occurring in the methylprednisolone cohort (0.7% vs 0%, $P = .1$). An additional PJI occurred outside of 90 days in a patient not receiving methylprednisolone (0.7% vs 0.2%, $P = .7$). Detailed information regarding infection cases and treatment regimens is listed in Table 4. Rates of other 90-day complications, including SSI (1.0% vs 1.4%, $P = .4$) and wound complication (1.0% vs 2.0%, $P = .4$), were also not significantly different between cohorts. There was a significantly lower rate of flexion contracture in the methylprednisolone cohort (0% vs 1.6%, $P = .036$). There were no significant differences in any complication rates at latest follow-up. Subgroup analysis of diabetic patients was also performed, and there were no differences in complication rates seen in this subgroup (Table 5).

Discussion

Postoperative use of adjuvant corticosteroids has shown promise in reducing postoperative pain and nausea after TKA.

Table 4
PJI cases breakdown.

Pt	Age	Medrol	Infection type	Organism	Time to infection (days)	Risk factors	Antimicrobial received	Surgical procedure	Outcome
1	75	Yes	Acute PJI	MSSA	35	None	IV cefazolin × 4 wks + PO cefadroxil × 1 y + PO rifampin 6 mo	I&D w/liner exchange	Laboratories normalized by 4 mo
2	71	No	Acute hematogenous PJI	MSSA	209	None	6 wks of cefazolin + rifampin	I&D w/liner exchange	Laboratories normalized by 4 mo
3	66	Yes	Acute PJI	*C acnes*	25	BMI 32.4	4 wks of ceftriaxone - > PO amoxicillin-clavulanate × 3 mo	I&D w/liner exchange	Asymptomatic f/u laboratories n/a

BMI, body mass index; *C acnes*, *Cutibacterium acnes*; f/u, follow-up; IV, intravenous; I&D, incision and drainage; MSSA, methicillin sensitive *Staphylococcus aureus*; n/a, not applicable; PJI, periprosthetic joint infection; PO, per os; Pt, patient.

While most of the existing evidence has focused on the efficacy and safety of perioperative intravenous administration of dexamethasone, newer evidence has suggested short courses of oral corticosteroids postoperatively might further reduce pain, nausea, and overall opioid consumption [27,28]. While chronic steroid use has been associated with increased risk of PJI, SSI, and wound dehiscence, the risks of short courses in the early postoperative period have not been well elucidated [25,29].

The primary finding of this study was that in the recent experience of 2 high-volume knee arthroplasty surgeons, no statistically significant differences were seen in the occurrence of PJI, SSI, or wound complication at 90 days following primary with the routine prescription of postoperative MTs. The results of this study, therefore, add to the limited literature regarding the safety of oral steroid use following primary TKA. This is particularly the case regarding concerns with potential significant risks associated with perioperative steroids.

Given that two-thirds of acute PJI cases occur due to intraoperative inoculation of microorganisms, it is at least plausible that an extended course of postoperative steroids might lead to increased infection via immune suppression in the acute postoperative period [30]. Recently, Piple et al. reported that oral prednisone administration following TKA was associated with higher rates of sepsis, PJI, and SSI [31]. However, they were unable to account for preoperative administration of prednisone, making interpretation of these data difficult [31]. However, a recent randomized controlled trial did not find a difference in complication rates after administration of an oral steroid for 4 days after TKA, although dexamethasone was used instead of methylprednisolone [32].

In the present study, there was no statistically significant difference in the rate of 90-day PJI or superficial SSI in patients receiving an MT compared to those who did not. Of 3 patients who developed PJI postoperatively, 2 occurred within 90 days and both received an MT, representing an incidence of 0.7%. While this indicates a potential signal for increased risk of PJI with methylprednisolone administration, it is important to note that despite the smaller cohort size, this incidence of PJI in the methylprednisolone cohort was still below prior estimates of PJI following primary TKA in the United States [33].

Another complication of concern in patients receiving postoperative steroids is the development of wound complications such as dehiscence or delayed closure. Steroids have been implicated in increased rates of wound dehiscence and impaired wound healing, especially in patients on chronic steroids [34]. The mechanism of this effect is thought to be due to inhibition of several growth factors and cytokines involved in fibroblast proliferation, collagen deposition, angiogenesis, and re-epithelization [35]. Nevertheless, current evidence suggests acute steroid administration perioperatively has no impact on wound healing [11,34]. Wang et al. found that even high-dose steroid administration for less than 10 days had no clinically important influence on wound healing outcomes [34]. In our study, we found no increased rates of wound complications in patients receiving methylprednisolone compared to those who did not, which is consistent with prior evidence.

A potential subgroup of patients hypothesized to be at greater risk of steroid-related complications are those with DM. Patients with DM are at intrinsically higher risk of several complications after TJA including both deep and superficial infection [36]. Postoperative hyperglycemia is a known risk factor for PJI after TKA; therefore, use of steroids in this population for multiple days may confer increased risk of complications due to increased postoperative hyperglycemia [37]. While administration of 1 or 2 doses of IV dexamethasone perioperatively has been shown to transiently increase blood glucose, it has not been associated with increased risk of wound infection or impaired healing, even in diabetic patients [38,39]. In accordance with prior evidence, subgroup analysis of diabetic patients in our study did not reveal increased rates of infection or wound complications receiving an MT. Only a small proportion of patients receiving methylprednisolone met criteria

Table 5
Subgroup analysis of outcomes in diabetic patients.

Outcome	No medrol,[a] n = 138	Medrol received,[a] n = 36	*P* value[c]
90-day			
PJI	0 (0)	0 (0)	-
SSI	1 (0.7)	1 (2.8)	.4
Wound complication	4 (2.9)	2 (5.6)	.6
VTE	0 (0)	0 (0)	-
Readmission	4 (2.9)	1 (2.8)	>.9
Flexion contracture	2 (1.4)	0 (0)	>.9
MUA	1 (0.7)	2 (5.6)	.11
Postoperative extension			>.9
0°-10°	136 (98.6)	36 (100)	
11°-20°	2 (1.4)	0 (0)	
>20°	0 (0)	0 (0)	
Postoperative flexion			>.9
0°-90°	15 (11.0)	1 (7.7)	
90°-120°	116 (83.7)	7 (53.9)	
>120°	8 (16.7)	5 (38.4)	
Latest follow-up			
Follow-up length	375 (269)[b]	272 (262)[b]	.05
Mechanical complication	0 (0)	0 (0)	-
Instability	2 (1.4)	2 (5.6)	.2
Revision	0 (0)	0 (0)	-
Periprosthetic fracture	1 (0.7)	0 (0)	>.9
Implant loosening	0 (0)	0 (0)	-
Vascular injury	0 (0)	0 (0)	-

MUA, manipulation under anesthesia; PJI, periprosthetic joint infection; SSI, surgical site infection; VTE, venous thromboembolism.
[a] n (%).
[b] Mean (SD).
[c] Welch 2-sample *t*-test; Fisher's exact test; Pearson's Chi-squared test.

for DM, and those who did had relatively well-controlled disease; therefore, more data is needed to ascertain whether poorly controlled DM may be a relative or absolute contraindication to a short duration of postoperative steroids after TKA.

There are several limitations to consider when interpreting the results of this study. As an observational study, there is potential for confounding. One such confounder was the influence of surgeon selection of patients who received the MT. Patients at higher risk of steroid-related complications such as poorly controlled diabetics were not given the steroid taper due to their perceived elevated risk, thus resulting in a methylprednisolone cohort that is healthier than the average patient population. Despite this, we did not note substantial differences in baseline comorbid status, and there was no difference in preoperative A1C among diabetic patients. Nevertheless, given the selection criteria used in this study, the results regarding the safety of oral steroid tapers should not be applied to patients with uncontrolled or complicated diabetes. Furthermore, we could not verify patient adherence in those prescribed the MT. Reduced adherence could lead us to falsely underestimate risk obtained from taking the full course of steroids, but this analysis is anticipated to closely mirror real-world adherence. Additionally, a substantial number of patient records were excluded due to lack of sufficient follow-up. However, it can be reasonably inferred that these patients did not experience significant complications as they did not choose to follow-up with their operating surgeon. We were also unable to assess information on patient-reported outcome measures, pain scores, or opioid consumption as these data were not prospectively collected for the majority of patients in the study and were not available upon review. As a result, we were unable to determine whether the addition of postoperative steroids provides clinical benefits that outweigh the small but legitimate potential for increased infection risk. Additionally, only a methylprednisolone steroid taper was evaluated in this study. There are other steroid compounds and dosages that may possess different safety profiles and efficacy following TKA. However, the primary goal of the study was to evaluate the potential risks associated with administration of a standard oral steroid rather than assess its efficacy with the purpose of subsequently conducting a randomized controlled trial to assess for reduction in postoperative pain and improvements in functional outcomes. Although to our knowledge this is the largest study to date on this topic, we do acknowledge that given the low event rate, we likely remain insufficiently powered to detect a statistically significantly increased risk of deep infection in the methylprednisolone cohort if one were to exist. Nevertheless, given the number of patients who received the steroid and low incidence of PJI, the findings of this study suggest that there are no substantially increased risks.

Conclusions

In conclusion, in this study, administration of an oral MT following TKA did not significantly increase rates of infection, wound complication, or any other major adverse event following primary TKA. More research is needed to further confirm the safety of this regimen and ascertain whether its use can serve to reduce pain, nausea, and opioid consumption postoperatively.

Conflicts of interest

Jacob Wilson is a paid consultant for Zimmer and holds stock or stock options in Accupredict. Ryan Martin received royalties from Restore3d and Enovis; is a paid consultant for Restore3D, Enovis, and DePuy. Ajay Premkumar holds stock or stock options in Accujoint, Osgenic, and Azra Care. Gregory Polkowski received royalties from Enovis; is a paid consultant for Enovis; and is a board member in American Association of Hip and Knee Surgeons.

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CRediT authorship contribution statement

Andrew A. Fuqua: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis. **Sean H. Gordon:** Writing – original draft, Data curation. **Anoop S. Chandrashekar:** Writing – review & editing, Data curation. **Bridger Rodoni:** Writing – review & editing, Methodology. **Thea Xerogaenes:** Data curation. **Ryan Martin:** Writing – review & editing, Project administration, Conceptualization. **James Roberson:** Resources, Investigation, Data curation, Conceptualization. **Gregory Polkowski:** Writing – review & editing, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Jacob M. Wilson":** Writing – review & editing, Resources, Project administration, Methodology, Investigation, Conceptualization. **Ajay Premkumar:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization.

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