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Corticosteroids in Glioblastoma Management: A Reconsideration of a 65-Year Practice

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Since Galicich and French[2] demonstrated dexamethasone's efficacy for peritumoral edema in 1961, corticosteroids have become standard therapy, prescribed to approximately 80% of patients with glioblastoma (GBM) perioperatively.[1,2] This practice originated from an uncontrolled study assessing short-term edema reduction—not survival or quality of life.[2] Remarkably, no adequately powered randomized trial has demonstrated prophylactic corticosteroid administration improves survival, quality of life, or functional outcomes. Yet reflexive prescription persists.

Contemporary evidence reveals a troubling paradox: While prescribed for palliation, corticosteroids are consistently associated with worse outcomes. Importantly, this association reflects complex confounding—patients requiring higher steroid doses often have greater tumor burden, more aggressive disease, or treatment-related injury. However, the consistency and magnitude of these associations, coupled with biological plausibility and evidence from minimization studies, suggests corticosteroids themselves contribute to worse outcomes beyond serving merely as markers of disease severity. Conversely, patients successfully managed without steroids demonstrate substantially better survival, lower infection rates, and superior quality of life. This disconnect between practice and evidence suggests pause and reconsideration.

Multiple large studies demonstrate consistent associations between corticosteroid use and reduced survival in GBM. Baseline dexamethasone use predicts consistent survival reduction with dose-dependent effects: Higher cumulative dexamethasone doses associate with progressively worse survival.[3-5] Although this article focuses on GBM, emerging evidence suggests similar corticosteroid-associated detriments in tumors metastatic to the brain with response reduction in immunotherapy candidates with concurrent steroid usage.[6,7]

Infection-related morbidity is substantial. A meta-analysis of steroid use and survival in GBM identified the reduction of overall survival (OS) and progression-free survival (PFS), summarizing the lymphopenia and metabolic effects (hyperglycemia) (as well as development of glioma stem cell-like phenotype) of a treatment resistance[8] associated with immune dysfunction. Historical data had noted high levels of *Pneumocystis jirovecii* pneumonia (PJP) in initial trials; recent data from patients with glioma receiving temozolomide and radiotherapy demonstrate PJP incidence <1% without prophylaxis (although prophylaxis itself causes severe toxicity in approximately 3% of patients).[9] Newer studies show increased infection rates per se with higher doses of steroids used, adjusted for age, Karnofsky performance status, RT, and temozolomide.[5] The evolving epidemiology likely reflects changing disease demographics, but nonetheless, infection-related mortality accounts for 12.5% of GBM deaths, the most common cause of death after tumor progression.[10] These are not inevitable malignancy consequences but iatrogenic complications occurring in patients with stable disease.

Quality-of-life assessments reveal the core paradox. Patients on chronic steroids report worse physical functioning (32% *v* 12% decline), emotional well-being (38% *v* 15% decline), and role functioning (41% *v* 18% decline) compared with steroid-free patients.[11] Insomnia affects 60%-80% versus 25%-30%, proximal myopathy 30%-60%, and cushingoid changes 40%-55%.[12-14]

Studies specifically examining steroid avoidance or early discontinuation demonstrate superior outcomes. Patients with GBM were evaluated who were either treated with dexamethasone pre/postoperatively *v*. not treated, with Kaplan-Meier analysis showing steroid use significantly associated with mortality ($P < .001$, log-rank test).[14] Díez Valle et al[15] implemented aggressive minimization protocols; 126 of 131 patients were successfully weaned within 4 weeks, with the mortality hazard ratio for patients in the steroid-weaned group of 0.47 (95% CI, 0.28 to 0.77, $P = .003$). Critically, total withdrawal of steroids was possible in 93% of patient cases in 2-4 weeks, demonstrating safety.

Effective alternatives exist. Vascular endothelial growth factor (VEGF) inhibitors, particularly bevacizumab, achieve successful steroid discontinuation in approximately 50% (95% CI, 16% to 66%) of patients within 2-4 weeks through vascular normalization.[16,17] Vredenburgh et al[18] reported 63% steroid tapering with median 4.5-month benefit. Recent systematic reviews and meta-analyses (2023-2024) demonstrate bevacizumab has an acceptable safety profile in patients with GBM, although adverse events warrant consideration.[19,20] Common complications include fatigue, thrombocytopenia, hypertension, and thromboembolic events. While grade 3-4 adverse events occur more frequently than with standard therapy alone, most are manageable with appropriate monitoring. Specific risks include hypertension (requiring medical management), proteinuria, and thromboembolic complications. Additionally, bevacizumab may promote more invasive, mesenchymal-like glioma phenotypes that could preclude clinical trial eligibility, and prolonged infusion center visits every 2-3 weeks that may affect quality of life compared with oral steroids.

Despite these considerations, multiple studies confirm bevacizumab's toxicity profile is acceptable and consistent with its established safety in clinical practice, particularly when weighed against the significant morbidity of prolonged high-dose corticosteroid therapy and preserves potential for immunotherapy.[17] Osmotic therapy provides acute rapid edema reduction without immunosuppression; hypertonic saline (23.4%) showed a 75% neurological improvement,[21] with 3% saline also noted to be effective, more so than mannitol.[22]

While many neuro-oncologists already practice thoughtful steroid minimization, the evidence suggests these approaches deserve broader implementation and more systematic application. Current practice varies considerably: An international survey found that perioperative dexamethasone dosing ranged from 4 mg to 24 mg daily, with no consensus on initiation criteria, duration, or taper schedules.[1] Moreover, the variability of steroid use preoperatively and postoperatively, during radiation therapy, and in adjuvant chemotherapy settings has recently been noted with differences in outcome, with patients not receiving dexamethasone during adjuvant therapy with significantly increased PFS/OS.[23] While recommendations for better studies on steroid usage in GBM have been called for,[24-26] to our knowledge, date no studies have been completed, although one ambitious study (RESDEX, Restrictive Use of Dexamethasone in Glioblastoma, ClinicalTrials.gov identifier:

NCT04266977) is ongoing.

Our anecdotal experience is similar. Variability is noted in dose (up to 24 mg dexamethasone daily), schedule (daily to four times daily), and duration (several weeks to without target dates of discontinuation or a steroid discontinuation plan). Prophylactic administration is common; upon discovery of GBM, the initiation of 4 mg four times daily of dexamethasone is virtually assured. Those implementing this include hospitalists, neurologists, neurosurgeons, radiation oncologists, and medical oncologists. In discussions, particularly early in course/presentation, or when patients enter into the emergency department, the rationale often relates to no known other alternatives. Particularly, in the inpatient setting, systematically providing recommendations on limiting or tapering steroids in these patient cases (especially in those without neurologic symptoms) and using alternatives when symptomatic is frequently questioned on the basis of the lack of familiarity of national society recommendations, use of VEGF inhibitors (and availability), and surprise for use of hypertonic agents (which many feel are used only in patients with brain herniation). Moreover, there is a significant amount of lack of knowledge on the adverse survival and clinical effects of steroids in patients with GBM.

Other sources of variability include institutional culture (community general hospitals *v* academic institutions), subspecialty training background (neurosurgeons *v* medical oncologists *v* neurologists *v* hospitalists), comfort with and knowledge of alternative edema management, and limited awareness of cumulative steroid harm data. Barriers to adoption include concern about acute neurological deterioration during taper or without steroids being used, the absence of randomized trial evidence directly comparing steroid minimization to standard practice, and the logistic challenges of implementing bevacizumab access for steroid-sparing purposes.

Given the compendium of published data and the observations in practice, several specific modifications are recommended (Table 1):

1. Symptom-driven rather than prophylactic initiation. Indeed, numerous societies (eg, Congress of Neurological Surgeons, The European Federation of Neurological Societies, and ASCO) have issued guidelines suggesting not to use prophylactic steroids in GBM.[24-26]
2. Aggressive dose minimization and early tapering. Given dose-dependent effects, initiating with 2-4 mg dexamethasone daily followed by aggressive poststabilization taper may reduce harm. Successful 2-4-week wean is both safe and beneficial.[15,19]
3. Selective infection prophylaxis. Given modern data showing PJP incidence <1% in patients with glioma without prophylaxis, routine prophylaxis requires reconsideration given 3% severe toxicity rates.[25] However, for high-risk patients (prolonged high-dose steroids, significant lymphopenia, and/or prior opportunistic infections), prophylaxis remains reasonable. This straightforward intervention could eliminate complications accounting for known susceptible patient deaths.
4. Finally, increased alternative utilization. Bevacizumab particularly and osmotic therapy acutely remain underutilized despite demonstrated steroid-sparing effects and superior safety, avoiding the potential for worse quality of life and OS.

Table 1. Recommendations and Implementation Strategies

Clinical Recommendation	Implementation Strategy

1. Symptom-driven rather than prophylactic initiation. Follow issued guidelines to not use prophylactic steroids in glioblastoma. 2. Aggressive dose minimization and early tapering. Successful 2-4-week wean is both safe and beneficial. 3. Selective infection prophylaxis. For high-risk patients (prolonged high-dose steroids, significant lymphopenia, or prior opportunistic infections), prophylaxis remains reasonable. 4. Increased alternative utilization. Bevacizumab particularly and osmotic therapy acutely remain underutilized despite demonstrated steroid-sparing effects and superior safety, avoiding the potential for worse quality of life and OS.	*Institutional level*: Incorporate steroid minimization protocols into order sets (default low-dose initiation, mandatory yet modifiable taper time lines) Multidisciplinary tumor board discussions to include steroid status as a treatment variable Quality improvement initiatives tracking steroid duration, cumulative dose, and infection rates for actionable feedback to prescribers *Education*: Training programs and Continuing Medical Education to incorporate evidence on steroid harm, dose minimization, and dose taper clinical plans QI ACGME programmatic projects on steroid stewardship as part of fulfilling residency/fellow requirements Emphasis on effective alternatives such as bevacizumab and osmotic therapy Continued efforts at the level of national societies on best practices with regard to steroid management in patients with brain tumor Patient-facing decision aids that present the trade-offs between short-term symptom relief and longer term risks for shared decision making

^ COLLAPSE

Abbreviations: ACGME, Accreditation Council for Graduate Medical Education; OS, overall survival; QI, quality improvement.

Encouraging broader adoption of these practices requires addressing both systemic and individual-level barriers (Table 1). At the institutional level, incorporating steroid minimization protocols into neuro-oncology order sets—with default low-dose initiation (eg, dexamethasone 4 mg daily) and mandatory taper time lines (obviously modifiable)—can shift prescribing from reflexive to deliberate. Multidisciplinary tumor board discussions could routinely include steroid status as a treatment variable, much as performance status and molecular markers are currently reviewed. Quality improvement (QI) initiatives tracking steroid duration, cumulative dose, and infection rates can provide actionable feedback to prescribers; since QI is part of many Accreditation Council for Graduate Medical Education (ACGME) training activities, this could become a programmatic project as part of fulfilling residency and/or fellowship requirements.

At the education level, in addition to QI noted, neurosurgery, neurology, and oncology training programs should incorporate the growing evidence on steroid harm into didactic curricula and continuing medical education, emphasizing that the traditional 16 mg daily regimen lacks rigorous evidentiary support and that lower doses achieve equivalent symptom control with fewer complications, notwithstanding the alternatives of VEGF inhibition more chronically and osmotic therapy acutely. Community oncologists, who manage most patients with GBM and may have less exposure to evolving neuro-oncology literature, represent a particularly important audience for dissemination efforts. Continued efforts at the level of national societies can also play a large role in educating clinicians on best practices with regard to steroid management in patients with GBM.

Finally, patient-inclusive decision aids that present the trade-offs between short-term symptom relief and longer term risks can facilitate shared decision making and empower patients to participate in steroid minimization strategies.

Sixty-five years after initial demonstration, accumulated evidence suggests more conservative corticosteroid prescribing may improve outcomes. Steroid use associates with reduced survival, increased infection-related mortality, and diminished quality of life. Conversely, successful avoidance demonstrates longer survival, dramatically lower infection rates, and better quality of life.

This is not wholesale abandonment advocacy—corticosteroids provide genuine neurologic benefit for many patients, particularly those with significant mass effect or in terminal phases. The goal is not elimination but judicious, symptom-driven use. Rather, it calls for critical reassessment of reflexive, prolonged prescription lacking evidentiary support. Implementation requires consideration of transitioning corticosteroids from default prescription to thoughtfully justified intervention. At follow-up, continuation should trigger "Why is this patient still on steroids?" rather than uncritical renewal.

Prospective trials would provide definitive evidence, albeit with pragmatic and ethical considerations. Notably, the RESDEX trial is attempting to answer this question, given their recent data noting disparity on use of steroids perioperatively versus during adjuvant therapy. However, observational study consistency and magnitude—coupled with biologic plausibility—suggest practice modifications may be warranted presently.

For a practice affecting many thousands annually, with potential to prevent early deaths through minimization alone, reconsideration is advisable for our patients. The question is not whether corticosteroids have a role but whether frequent prescribing practices, established premodern therapeutics, remain appropriate. The data suggest they do not.

Authors' Disclosures of Potential Conflicts of Interest

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