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# Corticosteroid use in pediatric neuro-oncology symptom management: A rapid review

**Neevika Manoharan, Nicole Armitage, and Claudia Virdun**

All author affiliations are listed at the end of the article

**Corresponding Author:** Neevika Manoharan, Kids Cancer Centre, Sydney Children's Hospital, High Street, Randwick, NSW 2031, Australia (Neevika.Manoharan@health.nsw.gov.au).



## Abstract

***Background.*** Corticosteroids are used routinely in pediatric patients with central nervous system tumors. However, the efficacy profiles of these medications, prevalence of adverse effects, dosing schedules, and impact on patients' quality-of-life are poorly elucidated. The aim of this study was to identify, appraise, and synthesize available international evidence regarding the role of corticosteroids in the symptom management of pediatric neuro-oncology patients.

***Methods.*** A rapid review of articles studying the role of corticosteroids in pediatric neuro-oncology was undertaken in August 2024. This study is reported using the PRISMA statement and was registered with PROSPERO (CRD42024567489). Five databases were searched, and data were analyzed using narrative synthesis.

***Results.*** Of the 1935 identified papers, 9 met the inclusion criteria (n = 6 retrospective cohort studies and n = 3 survey studies). Four key themes were identified in this rapid review: (1) variability in indication, dosing schedules, and prescribing practices for corticosteroids; (2) limited evidence available regarding symptomatic benefits from corticosteroid use; (3) adverse effects from prolonged corticosteroid use; and (4) clinicians recommend consensus guidelines to inform corticosteroid prescribing practice.

***Conclusion.*** As the first review utilizing systematic methodology exploring the topic of corticosteroid use in pediatric neuro-oncology, we identified a paucity of pediatric studies addressing corticosteroid efficacy. Dosing is variable, adverse effects are duration-dependent and multi-system and there is an urgent need for the development of guidelines to inform best practice. High-income countries and inpatient perioperative settings dominate the published literature. There is an absence of consumer voices addressing the impact on quality-of-life from corticosteroid use.

## Key Points

- Corticosteroids are used widely in pediatric neuro-oncology, particularly in the perioperative period, as an adjunct to radiotherapy and in the palliative setting.
- There is significant dosing variability with young children potentially receiving higher weight-based doses and no recommendations for corticosteroid cessation.
- There is underrepresentation of low- and middle-income countries (LMICs) in the published literature as well as absence of literature reporting specifically on corticosteroid use during radiotherapy. As such, it is essential that guidelines are developed to inform best practice that incorporate clinician judgement and consumer perspectives.

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## Importance of the Study

This is the first review utilizing systematic methodology exploring the role of corticosteroids in pediatric neuro-oncology in the perioperative, therapeutic, and palliative care settings. We identified four key themes in the literature regarding dosing variability, lack of evidence supporting symptomatic benefits, adverse effects from prolonged use, and an absence of consensus guidelines to inform prescribing practices. Future directions from this work would include the development of best practice guidelines for the use of corticosteroids utilizing co-design methodology and incorporation of corticosteroid dosing, weaning schedules, and stopping rules as secondary objectives in pediatric neuro-oncology clinical trials.

Central nervous system (CNS) tumors as a group are the second most common malignancy in paediatrics.[1,2] Although pediatric cancer mortality rates have decreased significantly in the last 50 years, this is primarily due to improvements in the survival outcomes for children with acute lymphoblastic leukemia (ALL).[3] Conversely, for children with CNS tumors, mortality rates have remained static over the last 20 years.[4] Consequently, brain tumors are the leading cause of cancer-related mortality in children.[3] In the context of high mortality rates in pediatric neuro-oncology, maintenance of quality-of-life (QOL) and minimizing distressing symptoms are major components of the holistic treatment for these patients.[5]

Corticosteroids are one of the most common medications in pediatric and adult neuro-oncology used in the perioperative setting as well as for management of symptomatic peritumoral edema throughout the disease course for many patients.[6] The term corticosteroid is used clinically to describe the therapeutic class of agents with glucocorticoid activity with these agents mimicking the endogenous steroid, cortisol.[7] Corticosteroids were first used for symptomatic management in patients with brain tumors with peritumoral edema in the 1950s,[8] with dexamethasone becoming the predominant corticosteroid in the 1960s due to its long biological half-life, high brain penetration, and predominant glucocorticoid activity with low mineralocorticoid activity.[9]

CNS tumors in children exhibit heterogenous symptomatology depending on the location of the tumor and proximity to anatomically eloquent structures of the brain or spine.[10,11] In addition, intracranial tumors often exhibit mass effect and are associated with tumor-related edema.[11] Corticosteroids are frequently used in the perioperative setting to manage tumor-related edema prior to, during, and after neurosurgical procedures to biopsy or resect the tumor.[12] Although the exact mechanism for its effect is unknown, corticosteroids appear to reduce peritumoral edema by a reduction in tumor capillary permeability and cytokine-driven blood-brain barrier breakdown.[13] While corticosteroids are a cornerstone in the neurosurgical management of peritumoral edema in pediatric neuro-oncology, it is important to note that this practice is extrapolated from adult neuro-oncology.[10,14]

Outside of the perioperative setting, corticosteroids are often used for symptom management throughout the disease course and in the palliative care setting in pediatric patients with CNS tumors.[14-16] Corticosteroids are routinely prescribed during radiotherapy, a treatment modality that routinely follows neurosurgery for local control in malignant brain tumors in children over 3 years old.[17,18] Radiotherapy can exacerbate peritumoral edema and cause radiation necrosis and the primary treatment modality used in these settings is corticosteroids.[19,20] In the palliative setting, corticosteroids are reported to be used for the management of a wide range of symptoms ranging from headaches to nausea and vomiting to localizing neurological signs and symptoms.[15] The efficacy with which these symptoms are managed by the use of corticosteroids is poorly elucidated and the balance between symptom relief and adverse effects of corticosteroids is challenging to quantify.[14,15]

The adverse effects of corticosteroids in pediatric patients with cancer are described predominantly in patients with acute lymphoblastic leukemia for whom corticosteroids are a key component of treatment protocols.[21-23] Side effects of corticosteroids are common, dose- and duration-dependent, and often affect multiple body systems.[22,23] Common side effects include weight gain, gastritis, mood and sleep disturbance, hypertension, and impaired glucose homeostasis.[24,25] Long-term side effects include avascular necrosis, cardiovascular disease, and cataracts.[24,26] Importantly, the use of corticosteroids can impact neuro-imagining in patients with CNS tumors. Accordingly, Response Assessment in Pediatric Neuro-Oncology (RAPNO) working groups have now recommended the documentation of corticosteroid dosing alongside neuro-imaging in pediatric neuro-oncology.[27,28] In pediatric neuro-oncology, the prevalence of corticosteroid-induced side effects are not well-studied and the impact of specific dosing schedules is poorly understood.[6,10,14] The aim of this study is to identify, appraise, and synthesize available international evidence regarding the role of corticosteroids in the symptom management of pediatric neuro-oncology patients. This will include identification of benefits of corticosteroid use in this setting as well as adverse effects, dosing, prescriber views, and patient and caregiver perception of corticosteroid use.

## Methods

### Design

A rapid review was conducted informed by the Hamel et al.definition of *"a rigorous and transparent form of knowledge synthesis that accelerates the process of conducting a traditional systematic review through streamlining or omitting a variety of methods to produce evidence for stakeholders in a resource-efficient manner."*[29] The only changes in process from a conventional systematic review were that

study selection and data extraction was led by one researcher (N.M.) with a second researcher (C.V.) reviewing 20% of titles, abstracts, and full texts. Any conflicts were resolved by consensus. Likewise, data extraction was led by one reviewer (N.M.) and checked at random by a second reviewer (C.V.). All other processes were conducted in line with systematic review methodology.[30] Analysis used a narrative synthesis strategy to integrate findings.[31] The narrative synthesis methodology was selected to allow for the variety of quantitative, qualitative, and mixed-method research available to answer the research question.[31] This rapid review was prospectively registered with PROSPERO (CRD42024567489).

### Eligibility Criteria

*Inclusion criteria:* Eligible studies were published between January 1990 to June 2024 in English peer-reviewed journals. All primary research (including qualitative, quantitative, or mixed methods primary research) where data of interest could be extracted was included.

*Population:* Pediatrics patients (aged 0-18 years of age) with benign and malignant CNS tumors internationally were included.

*Setting:* All patient care settings were included for this study including inpatient, outpatient, home-based care, and hospice-based palliative care.

*Intervention:* Use of corticosteroids (dexamethasone, prednisolone, methylprednisolone, and hydrocortisone) in the treatment of pediatric neuro-oncology patients.

*Exclusion criteria:*To ensure the inclusion of high-quality research, this review excluded case reports, opinion pieces, editorials, and publications that were abstracts without full-text or clinical trial protocols without publication of results. Studies of adult patients were excluded as were pediatric studies on the use of corticosteroids in other cancer populations (eg, patients with leukemia). Studies that did not address the research question as a primary endpoint of the study were excluded from analysis.

### Search Strategy and Information Sources

The search strategy was designed in consultation with a university librarian. It used a combination of MeSH terms and free text (keywords) utilizing Boolean Logic operators ("AND" and "OR").The search strategy is available as a Supplementary File (Supplementary Table S1). Five databases were searched including: Medline (via Ovid SP), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, Web of Science Core Collection (via ISI Web of Science), and Cochrane.

### Selection Process

Records returned from database searches were downloaded into Endnote 21 and duplicates removed. The primary researcher (N.M.) categorized all of the remaining retrieved records according to the agreed inclusion criteria registered with PROSPERO by review of abstracts and full-text review. A second reviewer (C.V.) audited 20% of the returned results to ensure accuracy. Calibration of reviewer categorization occurred via an Excel spreadsheet. Where differences occurred, these were resolved through consensus discussions. A PRISMA flow chart was created to capture the full-text reasons for exclusion.

### Data Collection Process

The primary reviewer (N.M.) extracted study data independently into an electronic spreadsheet in Microsoft Excel®. Extracted items included: author, year, country, aim, participants, setting, design, method of analysis, results, and conclusions. A second reviewer (N.A.) independently extracted data from 25% of the included full-text publications with extracted data compared between reviewers to ensure accuracy.

### Study Risk of Bias Assessment

To ensure inclusion of high-quality data, each included paper underwent risk of bias assessment by two reviewers (N.M., C.V.) using the Mixed Methods Appraisal Tool (MMAT).[32,33] This tool was selected for this rapid review as it ideal for assessment of quantitative, qualitative, and mixed-method research and allows us to use a singular tool for a risk of bias assessment of differing research methodologies.[32] Key parameters for determining high-quality publications were the clarity of research and the appropriateness of data collected to analyze the research questions. Further methodological quality criteria were included depending on study methodology (quantitative, qualitative, or mixed method). Two reviewers (N.M., C.V.) completed the MMAT independently and inter-rater reliability was analyzed.

### Data Analysis

A narrative synthesis strategy was employed to integrate key findings from quantitative, qualitative, and mixed-method studies.[31] Qualitative studies were analyzed using "line-by-line" thematic review in accordance with the Thomas and Harden's three-stage thematic synthesis.[34] Quantitative data, narrative descriptions, and raw quotes were extracted for analysis to ensure holistic content from each relevant publication was captured and informed overall synthesis. Descriptive statistics were used to capture the data heterogeneity in these studies.

## Results

A total of 1935 records were identified, of which 511 duplicates were removed, leaving 1424 records for screening. Thirty-eight manuscripts were sought for full-text review and ultimately, 9 met the criteria for inclusion in this review (Figure 1).[10,14,15,35-40] Of the 9 included studies,

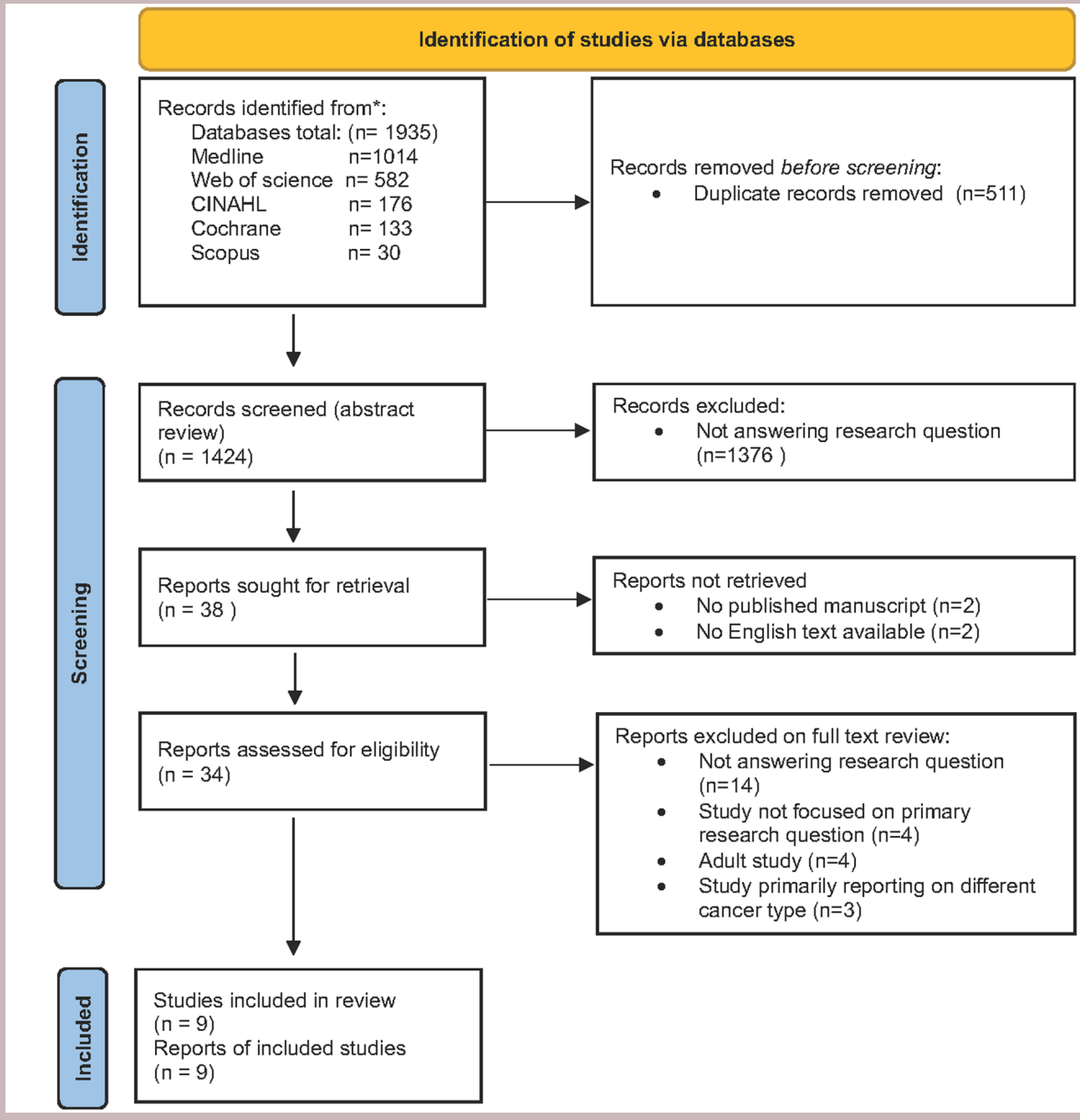


**Figure 1. PRISMA flow diagram.**

6 were retrospective single institution cohort studies[10,15,36-38,40] and the remaining three were international surveys.[14,35,39]

Seven studies utilized quantitative analysis and 2 studies captured quantitative and qualitative data as a part of a mixed methods approach. Most studies ($n$=6) collected data from hospital records of pediatric patients with brain tumors and the remainder ($n$=3) surveyed health professionals working in pediatric neuro-oncology. No studies reported on patient or parent/caregiver experiences of corticosteroid use in pediatric neuro-oncology.

All included studies had both clear research questions and appropriate methods to address stated questions. Risk of bias assessment utilizing the MMAT showed that the quantitative descriptive studies ($n$=7) were quality studies based on the key parameters of representation of target population, appropriate measurements regarding outcome or intervention, and accounting for confounding factors. Of the 2 mixed methods studies included, 1 failed to adequately report their rationale for mixed-method design and their data integration approach.[35] The inter-rater reliability utilizing the MMAT was 96% and in line with the inclusion criteria deigned *a priori*, all studies addressing the research question were included irrespective of their risk of bias assessment.

The majority of studies ($n$=8) were performed in high-income countries with universal health care and most of these were performed in Europe and the United Kingdom ($n$=6) (Table 1). Newly-diagnosed pediatric neuro-oncology patients in the perioperative setting were the focus of most studies ($n$=7), with the remaining 2 studies focusing on the palliative care setting for an incurable childhood brain

**Table 1.** Summary table of included studies.

| Author, (year), country | Participants | Setting | Design and method of analysis | Key study findings |
|---|---|---|---|---|
| Ayudhaya[10] (2022) Scotland | Pediatric patients (<19 years) with CNS tumors ($n$=127) | Inpatient neurosurgical tertiary hospital setting | Retrospective single-center study with quantitative analysis | • Median patient age=7 years and weight=27.9 kg<br>• Median dose and frequency were 4 mg and twice daily dosing<br>• Median daily dose (8 mg) did not correlate with patient weight<br>• Dexamethasone dose/kg inversely correlated with age (ie, 0-4 years received highest dose/kg)<br>• Median duration=8 days and route=intravenous<br>• Median weaning duration=11.5 days<br>• Length of corticosteroid administration correlated with risk of adverse events<br>• 19.7% incidence of adverse events (most common=weight gain)<br>• Proton pump inhibitors helped mitigate gastrointestinal side effects (64.2%)<br>• Dexamethasone well tolerated in the doses used in study<br>• Prescribing practices based on clinician preference and symptoms rather than patient age or weight |
| Elhemaly[15] (2022) Egypt | Pediatric patients (2-10 years) with DIPG ($n$=80) | Palliative care setting | Retrospective single-center cohort study with quantitative analysis | • Prevalent symptoms in last 12 weeks of life: headache, gait disturbance, vomiting, dysphagia, convulsions, constipation, disturbed conscious level, dysarthria, nausea<br>• Corticosteroids=the most common medication used (96%) for symptom management<br>• Gait disturbance and dysphagia improved with corticosteroid usage ($P$<.001)<br>• Corticosteroids effective in setting of disturbed consciousness when used alone (40%) or with mannitol (60%)<br>• Breathing difficulties, visual impairment, and motor weakness improved in some patients<br>• Adverse effects of corticosteroids=cushingoid facies, bony aches, mood swings, epigastric pain<br>• Corticosteroid dosing (0.25-1 mg/kg/days) and duration (days to months) were variable<br>• Corticosteroids efficiently managed many symptoms at end of life with tolerated side effects |
| Gorodezki[28] (2022) Germany | Pediatric patients (<18 years) with low-grade glioma ($n$=171) | Tertiary hospital setting | Retrospective single-center cohort study with quantitative analysis | • 34% of patients with gross total resection and 44% with incomplete resection had perioperative dexamethasone<br>• Indication=68% due to clinical or radiological hydrocephalus<br>• Mean dosing=0.27 mg/kg/days in 3 divided doses and mean duration=82 h with various length of tapering<br>• No significant difference in short- and long-term tumor growth rates<br>• Short-term perioperative dexamethasone use is safe in newly-diagnosed pLGG |
| Makwana[29] (2022) United Kingdom | Pediatric patients (<16 years) with posterior fossa tumors ($n$=30) | Inpatient tertiary hospital setting | Retrospective single-center cohort study with quantitative analysis | • Large doses used (stat) at initial presentation (average=9.15 mg or 0.31 mg/kg)<br>• All doses of dexamethasone reduced after review by neurosurgical team<br>• Average dose over 24 h (mg/kg) was highest in patients weighing 10-20 kg and lowest in patients >30 kg<br>• Proton pump inhibitor co-prescribed (80% of patients) to prevent gastrointestinal side effects<br>• No significant fluctuations in serum WCC or blood glucose taken within 24 h of admission<br>• Preoperative dexamethasone dosing does not always reflect clinical severity for patients with posterior fossa tumors |

Continued

**Table 1.** Continued

| Author, (year), country | Participants | Setting | Design and method of analysis | Key study findings |
|---|---|---|---|---|
| Carruthers[26] (2021) United Kingdom | Neuro-oncology providers from international pediatric neurosurgical centers ($n$=9) Pediatric patients (<19 years) undergoing neuro-oncology procedures ($n$=64) | International survey and inpatient tertiary hospital setting | International multicenter survey study and retrospective single-center cohort study with mixed methods analysis | • No surveyed pediatric neurosurgical center had established guidelines for corticosteroid prescribing<br>• Variability in corticosteroid (majority dexamethasone) and indication for use (all tumor surgeries versus case-by-case)<br>• Dexamethasone dosing was variable (0.2-0.5 mg/kg/day)<br>• Not all centers weaned corticosteroids and weans ranged from 3 days to 3 weeks<br>• Higher dose and longer duration used for symptoms, edema, hydrocephalus, or residual tumor<br>• Local service review showed 30% of patients had no corticosteroids or only single intraoperative dose<br>• Study identified significant heterogeneity and lack of standardization in corticosteroid use |
| Malbari[30] (2020) USA | Neuro-oncology providers from pediatric neuro-oncology consortia ($n$=76) | International survey | International multicenter survey study with quantitative | • Respondents = 50% pediatric oncologists, 25% neurosurgeons, 11.8% nurse practitioners, 6.6% pediatric neurologists<br>• Proportion of providers who would start corticosteroids differed between scenarios<br>• Majority would commence corticosteroids for vasogenic edema (96.1%) and obstructive hydrocephalus (72.4%)<br>• Differences in preferences for loading doses and dosing schemes<br>• Odds of starting corticosteroids sooner if patient presented with neurological symptoms<br>• 4.7× greater if provider received formal training in neuro-oncology<br>• Length of time to wean off = between 5 and 7 days |
| Veldhuijzen[14] (2016) Netherlands | Neuro-oncology providers who specialize in care of pediatric patients with DIPG ($n$=150) | International survey | International and multicenter survey study and review of relevant literature with mixed methods analysis | • Providers only treated median 2 DIPG patients/year (11 professionals who treated >8 or more/year)<br>• 93% reported no guideline for the prescription of corticosteroids in their institution<br>• 91% prescribe dexamethasone<br>• Corticosteroid therapy initiated by pediatric oncologist (82%) or radiotherapist (18%)<br>• Corticosteroids prescribed throughout entire disease course—mainly driven by clinical symptoms<br>• Route = oral (majority)<br>• Heterogenous dosing = 1.5 mg/m$^2$ to 52.5 mg/m2/day (median = 8.5 mg/m$^2$/day)<br>• Taper = 75% always taper, remainder variable<br>• Common side effects (>85%) = mood changes, obesity, food craving, personality changes, depression, Cushing's syndrome, insomnia, muscle atrophy, skin thinning, hypertension, edema<br>• 68% = corticosteroids of benefit in symptom management in DIPG<br>• 46% = side effects do not outweigh benefits<br>• 77% = corticosteroid alternatives urgently needed<br>• Literature review ($n$=14) showed most papers describe use of dexamethasone and dosing, minimal data on efficacy and side effects described across multiple studies |
| Muller[31] (2003) Germany | Pediatric patients (<18 years) with craniopharyngioma requiring neurosurgical procedures ($n$=60) | Tertiary hospital setting | Retrospective single-center cohort study with quantitative analysis | • Cumulative dose of perioperative dexamethasone correlated with maximum increase in body mass index (BMI) during first year after surgery<br>• No correlation between cumulative dexamethasone dose and BMI at final visit<br>• Perioperative dexamethasone treatment has an impact on short-term weight gain but not long-term obesity in patients with craniopharyngioma |

Continued

**Table 1.** Continued

| Author, (year), country | Participants | Setting | Design and method of analysis | Key study findings |
|---|---|---|---|---|
| Glaser[27] (1997) Canada | Pediatric patients with central nervous system tumors ($n$=62) | Tertiary hospital setting | Retrospective single-center audit study with quantitative analysis | • Indication for corticosteroid use=raised ICP (68%) in majority of patients<br>• Corticosteroids frequently used for long periods with 25% of courses were >4 weeks<br>• Beneficial in management of raised ICP but need to balance this against frequently observed severe side effects<br>• Adverse effects seen with long courses= severe mood changes, behavioral changes, insatiable appetite, weight gain, cushingoid facies, altered body habitus causing distress, peptic ulceration and gastritis, mucocutaneous candidiasis<br>• Long-term adverse effects: proximal myopathy, cataracts, osteoporosis, Addisonian crisis<br>• Recommended dosing for corticosteroid use provided by authors=dexamethasone for raised ICP/preparation for neurosurgery at 0.5 mg/kg/day in divided doses (trial of 3-4 days, 16 mg/days max), smaller dose if possible |

tumor, diffuse intrinsic pontine glioma (DIPG).[14,15] No studies reported specifically on the use of corticosteroids during radiotherapy for pediatric patients. All studies were performed in specialist pediatric neurosurgical, neuro-oncology, or palliative-care settings with all studies that reported on patient data being derived from the inpatient hospital setting. Pediatric patients with a variety of tumor types were captured across studies including DIPG, low-grade glioma, medulloblastoma, ependymoma, and craniopharyngioma.

Data were collected from a combined total of 594 pediatric neuro-oncology patients, 226 health professionals working in pediatric neuro-oncology, and 9 international neurosurgical centers. Narrative synthesis of the data extracted generated 4 key themes identified across the studies pertaining to the role of corticosteroids in pediatric neuro-oncology.

## *Variability in Indication, Dosing Schedules, and Prescribing Practices for Corticosteroids Described*

The indication for corticosteroid use in pediatric neuro-oncology patients varied from being utilized preemptively in the perioperative setting,[35] to being used for the management of symptomatic vasogenic edema, raised intracranial pressure (ICP), or hydrocephalus in the perioperative setting,[36,37,39] to being used for symptomatic management (eg, headache, vomiting) in the palliative care setting.[14,15] Dexamethasone was the most common corticosteroid utilized across the studies reported[10,14,35-40] and route of administration was most commonly intravenous in the perioperative setting[10] and predominantly oral in the palliative care setting.[14]

Corticosteroid prescribing was initiated predominantly by neurosurgeons in the perioperative setting[38] and by a pediatric neuro-oncologists in the setting of patients with DIPG.[14] One study found the odds of starting corticosteroid in a patient with neurological symptoms to be 4.69 times more likely (CI 1.54-14.34) among providers who had formal training in neuro-oncology compared to those who did not have formal training.[39]

Prescribing practices and dosing of dexamethasone varied widely across studies. Dosing ranges reported in the included studies were 0.2-0.5 mg/kg/day[10,14,35,37,38] with an average loading dose of 9.15 mg in 1 study (0.31 mg/kg).[38] Importantly, the median daily dose of dexamethasone (8 mg/day) did not always correlate with weight and that patients in the 0-4 years old age group received the largest mg/kg dosing of dexamethasone.[10] Multiple studies postulated that this variability was due to prescriber preferences and clinical judgement rather than the use of dosing schemas or guidelines.[10,37,38] Duration of corticosteroid use varied considerably across studies and tapers were not universally used.[14,35] Although some studies reported a median duration of corticosteroid use between 3 and 8 days[10,14,39] and weaning schedules between 5 and 21 days,[10,35,39] another study showed that 1 in 4 patients will have a corticosteroid course greater than 4 weeks.[36] No studies described criteria for the cessation of steroids. Heterogeneity in corticosteroid prescribing practices was not always accounted for by the clinical symptoms in the patients.[38,39] Veldhuijzen et al.reported on corticosteroids being prescribed for entire disease courses for patients with DIPG without a clear correlation with symptoms.[14]

## *Limited Evidence Available Regarding Symptomatic Benefits from Corticosteroid Use*

Most of the included studies ($n$=7) reporting on corticosteroid use in pediatric neuro-oncology, did not report on their efficacy.[10,35,37-40] These studies instead focused on dosing and weaning schedules, duration of use, adverse effects, and prescriber preferences. Perioperative symptoms for which

dexamethasone was used were headache and vomiting associated with raised ICP or peritumoral edema with the majority of prescribers (96.1%) reporting efficacy for these indications.[36,39] In the palliative care setting for patients with DIPG, 1 study reported on corticosteroids as the most common medication used in symptom management in the last 12 weeks of life in a retrospective cohort study.[15] In this study, the authors reported that gait disturbance and dysphagia showed improvement with corticosteroid usage ($P<.001$) and that corticosteroids were effective in patients with disturbed consciousness when used as monotherapy (40%) or with mannitol (60%).[15] Additionally, 68% of prescribers in a survey study of patients with DIPG reported corticosteroids were of benefit in symptom management in DIPG but 77% reported corticosteroid alternatives were urgently needed due to adverse effects.[14]

### *Adverse Effects from Prolonged Corticosteroid Use*

Adverse effects as a result of corticosteroid use in children with brain tumors were reported as a concern in multiple included studies.[14,35,36] These adverse effects were described as common (occurring in >85% of patients) and included mood changes, obesity, hyperglycemia, food craving, personality changes, depression, sleep disturbance, Cushing's syndrome, insomnia, muscle atrophy, skin thinning, hypertension, and edema.[14,36] The length of corticosteroid administration corelated with risk of adverse events.[10] Veldhuijzen et al. reported that 46% of prescribers surveyed reported that the side effects of corticosteroid use outweighed the potential benefit in patients with DIPG.[14] None of the included studies reported on patient or caregiver perspectives on adverse effects of corticosteroids.

Studies reporting on perioperative short-term corticosteroid use, described dexamethasone as being well-tolerated with limited adverse effects observed.[37,38] These studies also reported on co-prescription of a proton pump inhibitor to mitigate the potential gastrointestinal side effects of dexamethasone (in 64.2%-80% of patients).[10,38] In patients with craniopharyngioma dexamethasone has a significant impact on short-term weight gain but not long-term obesity.[40] As such, in the perioperative setting, the included studies reported manageable side effects of dexamethasone,[10,37,38,40] whereas in the setting of prolonged use in the palliative care setting, the reported prevalence of side effects was greater.[14,36]

### *Clinicians Call for Expert Consensus Guidelines to Inform Corticosteroid Prescribing Practice*

A consistent theme across many ($n=7$ of 9) of the included publications is the lack of established protocols or guidelines for corticosteroid prescribing in pediatric neuro-oncology and the need for guidelines to allow some standardization in variable prescribing practices.[10,14,35-39] An international survey study of 150 pediatric neuro-oncology specialists found that 93% of respondents reported no established guidelines for the prescription of corticosteroids for pediatric neuro-oncology patients in their institution.[14] Another international survey study of 9 international neurosurgical centers reported that none of these institutions had established guidelines for the prescription of corticosteroids.[35] Some authors[35,36] proposed guidelines based on the expert opinions of the authorship or local expertise encompassing dosing guidelines, indications, and weaning suggestions. Others suggest that large collaborative groups (eg, SIOPe DIPG Registry[41]) may be best positioned to develop these guidelines.[14] It was noted that clinical trials answering this research question would be too challenging to perform and authors proposed an expert panel approach as an alternative.[39]

## Discussion

To our knowledge, this rapid review investigating the role of corticosteroids in the symptomatic management of patients with childhood CNS tumors is the first utilizing systematic methodology to explore this area. Strikingly, only 9 studies met inclusion for this review, with a clear predominance of high-income countries and inpatient perioperative treatment settings. This small sample size undoubtedly reflects the paucity of published literature on this topic and highlights corticosteroid use in pediatric neuro-oncology as an area desperately requiring further study.

The prevalent use of corticosteroids as a therapeutic agent in neuro-oncology over the last half century ensures that it is now firmly standard of care for pediatric patients with brain tumors.[6,42,43] Despite this widespread use, it is important to note that dedicated studies on the role of corticosteroids in neuro-oncology are largely adult studies from which pediatric practice has been extrapolated.[13,44,45] In adult studies, there has been clear demonstration that the side effects of corticosteroid use are a significant problem that has a lasting functional impact on patient QOL[46-48] and the need to balance adverse effects against efficacy has been emphasized.[6,49] The Jumpstarting Brain Tumor Drug Development Coalition (JSBTDDC) is a coalition of Neuro-Oncology societies and research groups focused on evaluating and improving brain tumor clinical trials. The importance of corticosteroid side effects and functional and patient-reported outcomes (PROs) has been emphasized as a key Clinical Outcome Assessment by the JSBTDDC workshop with the USA Food and Drug Administration.[50] The absence of parent and caregiver perspectives on adverse effects and QOL with the use of corticosteroids indicates the urgency for dedicated consumer studies in this area that has been identified as a key priority for the field of pediatric and adult neuro-oncology.

It is apparent from our review that variable dosing practices, weaning regimens, and indications exist for the use of corticosteroids in pediatric neuro-oncology and standardized guidelines or expert consensus are urgently needed to address this variability. Importantly, the doses of corticosteroid prescribed did not always correlate with patient weight, with younger children receiving higher mg/kg doses of dexamethasone[10] which could result in a significant increase in corticosteroid-related adverse effects for young children. This practice, as well as the overall variability in prescribing, is likely the result of individual practitioners utilizing clinical judgement on a "case-by-case" basis rather than pharmacology-driven prescribing practices.[7] A challenge in developing a guideline to standardize corticosteroid use in pediatric

neuro-oncology would be incorporating clinician discretion and clinical judgment which remain paramount in the practice of pediatric neuro-oncology. In addition, the lack of criteria for cessation of corticosteroids and the impact of formal neuro-oncology training on likelihood of corticosteroid prescription highlights the need for expert guidelines encompassing safe prescribing practices.

It is important to acknowledge the strengths and limitations of this review. Our study was strengthened by utilizing and strictly adhering to the PRISMA guidelines.[51] Moreover, we utilized multiple reviewers to ensure scientific rigor. Furthermore, we excluded studies whereby our primary research question was not a key outcome of interest to ensure high-quality accurate data was extracted and excluded study-types that were not of high-quality (eg, case reports and editorials). Methodologically, our review encompassed studies that were largely retrospective or survey-based, single institution or region and predominantly focused on populations in Europe and The United Kingdom.[10,14,35-40] Importantly, there were no comprehensive prospective studies, randomized clinical trials or systematic reviews on this topic and only one study (from Egypt) captured a LMIC perspective.[15] Moreover, none of the published studies explored corticosteroid use as an adjunct to radiotherapy or quantified the burden of corticosteroid adverse effects as the primary research question. Although, these can be seen as key limitations to this work that may impact generalizability of the findings, it is important to note the context in pediatric neuro-oncology, a rare patient population wherein randomized trials and systematic reviews are scarce for all research questions.[52] Undoubtedly, one of the most significant findings and limitations of our review is the absence of patient, parent and caregiver perspectives on the benefits and sequelae of corticosteroid use in patients with brain tumors and the impact on their QOL as well as their families.

This study has identified multiple key areas that are ripe for future research opportunities that have the potential to impact both clinical practice in pediatric neuro-oncology. Firstly, a consensus guideline to guide clinical practice in corticosteroid use in neuro-oncology patients is a priority. Use of the Delphi methodology would be ideal for this research area and could be executed internationally via the collaborative pediatric neuro-oncology community.[53] Although a dedicated clinical trial exploring corticosteroid dosing, adverse effects, weaning, and stopping criteria may be challenging to execute, the incorporation of corticosteroid clinical and radiological endpoints as secondary objectives in early-phase clinical trials would be valuable. Another crucial area of research stemming from our study is the need to explore patient and caregiver perspectives on corticosteroids in pediatric neuro-oncology as this was arguably the most significant limitation in the published literature. The incorporation of PROs regarding corticosteroid use in clinical trials as well as dedicated consumer studies are required to fill this gap.

## Conclusions

Although corticosteroids are widely used in clinical practice in pediatric neuro-oncology in the perioperative phase, throughout treatment and in palliative care, there is a paucity of studies reporting on the efficacy of corticosteroids in this setting and the balance between the benefits of use and the significant side effects of prolonged use. In this review, we highlight the significant variability in dosing, courses, tapering, and duration of dexamethasone among clinicians in the field of pediatric neuro-oncology and the urgent need to develop guidelines or expert recommendations around the use of corticosteroids. There is no published data specifically exploring corticosteroid use in radiotherapy in the pediatric neuro-oncology population and underrepresentation of LMICs in the published literature. Despite a key paradigm in pediatric neuro-oncology being that of quality-of-life, there is a complete absence of patient and caregiver perspectives to address the question of the precarious balance that is the risks and benefits of corticosteroid use in this population.

## Supplementary Material

Supplementary material is available online at *Neuro-Oncology Practice* (https://academic.oup.com/nop/).


## Keywords

corticosteroids | neuro-oncology | pediatrics | symptom management


## Author Contributions

Review topic conceptualized by N.M. and C.V. Article selection and screening performed by N.M. and verified by C.V. Data collection performed by N.M. and verified by N.A. Risk of bias performed by N.M. and C.V. Data analysis and article writing by N.M. All authors critically reviewed and revised the article. All authors approved the final article as submitted and agree to be accountable for all aspects of the work.

## Conflict of Interest Statement

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## Ethics

Not applicable for this review paper as not utilizing experimental investigations of human subjects.

## Data Availability

Table to search strategy included as Supplementary Table S1.

## Affiliations

Kids Cancer Centre, Sydney Children's Hospital, Randwick, Australia (N.M.); School of Women's and Children's Health, UNSW Sydney, Kensington, Australia (N.M., N.A.); Children's Cancer Institute, Kensington, Australia (N.M.); Department of Palliative Care, Sydney Children's Hospital, Randwick, Australia (N.A.); College of Nursing and Health Sciences, Flinders University, Adelaide, Australia (C.V.); Flinders Research Centre for Palliative Care, Death and Dying, Flinders University, Adelaide, Australia (C.V.); Faculty of Health, Cancer and Palliative Care Outcomes Centre, Queensland University of Technology (QUT), Brisbane, Australia (C.V.); Improving Palliative, Aged and Chronic Care through Clinical Research and Translation (IMPACCT), Faculty of Health, University of Technology Sydney (UTS), Sydney, Australia (C.V.)

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