Office of Evidence Based Practice (EBP) – Critically Appraised Topic (CAT): Dexamethasone and Brain Tumors

Specific Care Question

In pediatric patients with brain tumors, does the use of dexamethasone as an antiemetic versus not using dexamethasone result in decreased overall survival or tumor recurrence?

Recommendations Based on Current Literature (Best Evidence) Only

A conditional recommendation is made against the routine use of dexamethasone as an antiemetic in patients with brain tumors, based on review of current literature by the Department of EBP. Consideration could be given to dexamethasone use as an antiemetic in cases of severe refractory chemotherapy-induced nausea/vomiting after other agents have proven ineffective. The overall certainty in the evidence is very low. Due to the lack of evidence for safety concerns of dexamethasone in the treatment of nausea and vomiting in pediatric patients with brain tumors, this review included studies that used dexamethasone for the treatment of cerebral edema in adult and pediatric patients with brain tumors. Three of the four included studies found a significant associated decrease in overall survival rates of patients treated with dexamethasone. This concurs with the Multinational Association of Supportive Care in Cancer (MASCC), which recommends against the use of dexamethasone in children receiving radiation and chemotherapy treatment of brain tumors.

Literature Summary

Background. Dexamethasone has been shown to be an effective treatment for nausea and vomiting in patients with cancer (Phillips et al., 2016). While adding dexamethasone improves control of vomiting, clinical studies have not found an association with steroids as an antiemetic and poor outcome (Phillips et al., 2016). Current antiemetic practice guidelines from the American Society of Clinical Oncology (ASCO) (Hesketh et al., 2017) recommend the use of a 5HT3 receptor antagonist, dexamethasone, plus aprepitant for children receiving highly emetogenic chemotherapy (HEC). The guideline makes no mention of treatment for pediatric patients with brain tumor. It does recommend adult patients who are treated with radiation therapy to the brain should be offered rescue dexamethasone therapy. The use of dexamethasone is not without its concerns in patients with brain tumors. This is due to the concern for potential impairment of the blood–brain permeability, concerns regarding potential interference with apoptosis, and fungal infection (Dupuis, Roscoe, Olver, Aapro, & Molassiotis, 2017). A guideline by MASCC recommends against or strongly discourages the use of dexamethasone in children receiving radiation and chemotherapy treatment of brain tumors (Dupuis et al., 2017).

Dexamethasone is also commonly used in patients with brain tumors to reduce cerebral edema (Hui, Rudra, Ma, Campian, & Huang, 2019). However, the use of dexamethasone for the treatment of cerebral edema has come under scrutiny, due to the same side-effects when used as an antiemetic (Wong, Lok, Gautam, & Swanson, 2015). Due to the paucity of evidence in the efficacy of dexamethasone in the treatment of nausea and vomiting in pediatric patients with brain tumors, this review included studies that reviewed dexamethasone for the treatment of cerebral edema in patients with brain tumors. This review will summarize current literature on the topic.

Study characteristics. The search for suitable studies was completed on November 23, 2019. J. Thompson, MD reviewed the 99 titles and/or abstracts in December 2019 and March 2020 and identified two guidelines and twenty single studies believed to answer the question.[a] J. Thompson, MD reviewed the articles twice to assure appropriate literature was selected for this topic. After an in-depth review of the guidelines[d] and single studies[b], two guidelines (Dupuis et al., 2017; Hesketh et al., 2017) and four cohort studies (Dubinski et al., 2018; Hui et al., 2019; Shields et al., 2015; Wolff, Hauch, Kuhl, Egeler, & Jurgens, 1998) answered the question and are included in this review (see Figure 1).

The AGREE II[d] tool was used to assess the guidelines. Both guidelines were selected with the recommendation to be used without modification (Dupuis et al., 2017; Hesketh et al., 2017) (see Table 1).

Summary by outcome

Overall survival. Four cohort studies (Dubinski et al., 2018; Hui et al., 2019; Shields et al., 2015; Wolff et al., 1998) measured overall survival (OS), (N = 401). A meta-analysis was not completed due to the heterogeneity of the included studies. In a study of children with brain tumors (n = 20) methotrexate with dexamethasone versus methotrexate without dexamethasone was compared (Wolff et al., 1998). There were no therapy related deaths in either group during chemotherapy. Dubinski et al. (2018) reviewed the effects of dexamethasone-induced leukocytosis on OS in adults (n = 59) with newly diagnosed glioblastoma (GBM). The study reported the presence of dexamethasone-induced leukocytosis decreased OS, Hazard ratio (HR) = 2.25, 95% CI [1.15, 4.38], p < .001. Hui et al. (2019) compared high versus low corticosteroid exposure during chemotherapy on adults (n =

319) with newly diagnosed GBM. High-dose corticosteroid cohort was independently associated with decreased OS, *HR* = 1.131, 95% CIs [1.059, 1.208]. Shields et al. (2015) reviewed the effects of dexamethasone on OS adults with newly diagnosed GBM (*n* = 73). Patients weaned off dexamethasone had an OS of 22.5 months compared to 12.7 months for those not weaned off dexamethasone, *p* = .02.

Certainty of the evidence for overall survival. The certainty of the body of evidence was very low based on four factors[c]: *within-study risk of bias*, *consistency among studies, directness of evidence*, and *precision of effect estimates*. The body of evidence was assessed to have serious risk of bias, serious inconsistency and very serious indirectness. Risk of bias was serious due to the studies were all retrospective cohorts. The consistency was serious due to the heterogeneity of the study designs. Indirectness was very serious due to three of the four studies included adults (Dubinski et al., 2018; Hui et al., 2019; Shields et al., 2015) and none of the studies used corticosteroids as an antiemetic.

Identification of Studies which database?

Search Strategy and Results (see Figure 1)

Pubmed

("brain tumor*"[tiab] OR "Brain Neoplasms"[Mesh]) AND "Dexamethasone/adverse effects"[Mesh] NOT "Case Reports" [Publication Type]

("brain tumor*" OR "Brain Neoplasms"[Mesh]) AND ("Antineoplastic Agents"[Mesh] OR "Nausea/chemically induced"[MeSH] OR "Vomiting/chemically induced"[MeSH]) AND ("Antiemetics"[Mesh] OR ("Dexamethasone"[Mesh] AND ("antiemetics"[Mesh] OR "Vomiting/prevention and control"[Mesh] OR "Nausea/prevention and control"[Mesh])))

"Antineoplastic Agents/adverse effects"[Majr]) AND ("Antiemetics/therapeutic use"[Majr] OR ("Dexamethasone/therapeutic use"[Majr] AND ("antiemetics"[Majr] OR "Vomiting/prevention and control"[Mesh] OR "Nausea/prevention and control"[Mesh]))) AND (child OR children OR pediatr* OR paediatr* OR childhood)

Records identified through database searching *n* = 99

Studies Included in this Review

Citation	Study Type
Dubinski et al. (2018)	Cohort
Dupuis et al. (2017)	Guideline
Hesketh et al. (2017)	Guideline
Hui et al. (2019)	Cohort
Shields et al. (2015)	Cohort
Wolff et al. (1998)	Cohort

Studies Not Included in this Review with Exclusion Rationale

Citation	Reason for exclusion
Basch et al. (2011)	Outdated ASCO Guideline
Duggin et al. (2014)	Participants did not receive dexamethasone
Dupuis et al. (2013)	Does not discuss brain tumor patients
Hempen, Weiss, and Hess (2002)	Outcome of interest not reported
Ikeda, Carson, Lauer, and Long (1993)	Non-human
Kostopoulou et al. (2018)	Non-human
Matsuda et al. (2016)	Outcome of interest not reported

Nahaczewski, Fowler, and Hariharan (2004)	Review article
Nestler, Winking, and Boker (2002)	Non-human
Patel, Paw Cho Sing, and Dupuis (2019)	Outcome of interest not reported
Phillips et al. (2016)	Outcome of interest not reported
Pitter et al. (2016)	Non-human
Schulte (1983)	Non-English
Takeuchi et al. (2016)	Does not discuss brain tumor patients
Waxman, Beldon, Richli, Tanasescu, and Siemsen (1978)	Outcome of interest not reported

Methods Used for Appraisal and Synthesis

[a]Rayyan is a web-based software used for the initial screening of titles and / or abstracts for this analysis (Ouzzani, Hammady, Fedorowicz & Elmagarmid, 2017).

[b]Review Manager (Higgins & Green, 2011) is a Cochrane Collaborative computer program used to assess the study characteristics as well as the risk of bias and create the forest plots found in this analysis.

[c]The GRADEpro Guideline Development Tool (GDT) is the tool used to create the Summary of Findings table(s) for this analysis.

[d]The Appraisal of Guidelines Research and Evaluation II (AGREE II) is an international instrument used to assess the quality and reporting of clinical practice guidelines for this analysis (Brouwers et al. 2010).

[e]The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram depicts the process in which literature is searched, screened, and eligibility criteria is applied (Moher, Liberati, Tetzlaff, & Altman, 2009).

[a]Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews, 5*(1), 210. doi:10.1186/s13643-016-0384-4

[b]Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions [updated March 2011]* (Version 5.1.0 ed.): The Cochrane Collaboration, 2011.

[c]GRADEpro GDT: GRADEpro Guideline Development Tool (2015). McMaster University, (developed by Evidence Prime, Inc.). [Software]. Available from gradepro.org.

[d]Brouwers, M.C. et al. for the AGREE Next Steps Consortium. (2010) AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *Canadian Medical Association Journal, 182*, E839-842. Retrieved from https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf

[e]Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097 **For more information, visit www.prisma-statement.org.**

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Acronyms Used in this Document

Acronym	Explanation
AGREE II	Appraisal of Guidelines Research and Evaluation II
ASCO	American Society of Clinical Oncology
ASL	Acute severe lymphopenia
BEZ	Bevacizumab
CAT	Critically Appraised Topic
DEX	Dexamethasone
EBP	Evidence Based Practice
GBM	Glioblastoma
GTR	Gross-total resection
HEC	Highly emetogenic chemotherapy
MASCC	Multinational Association of Supportive Care in Cancer
MXT	Methotrexate
OS	Overall Survival
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PFS	Progression-free survival
TMZ	Temozolomide

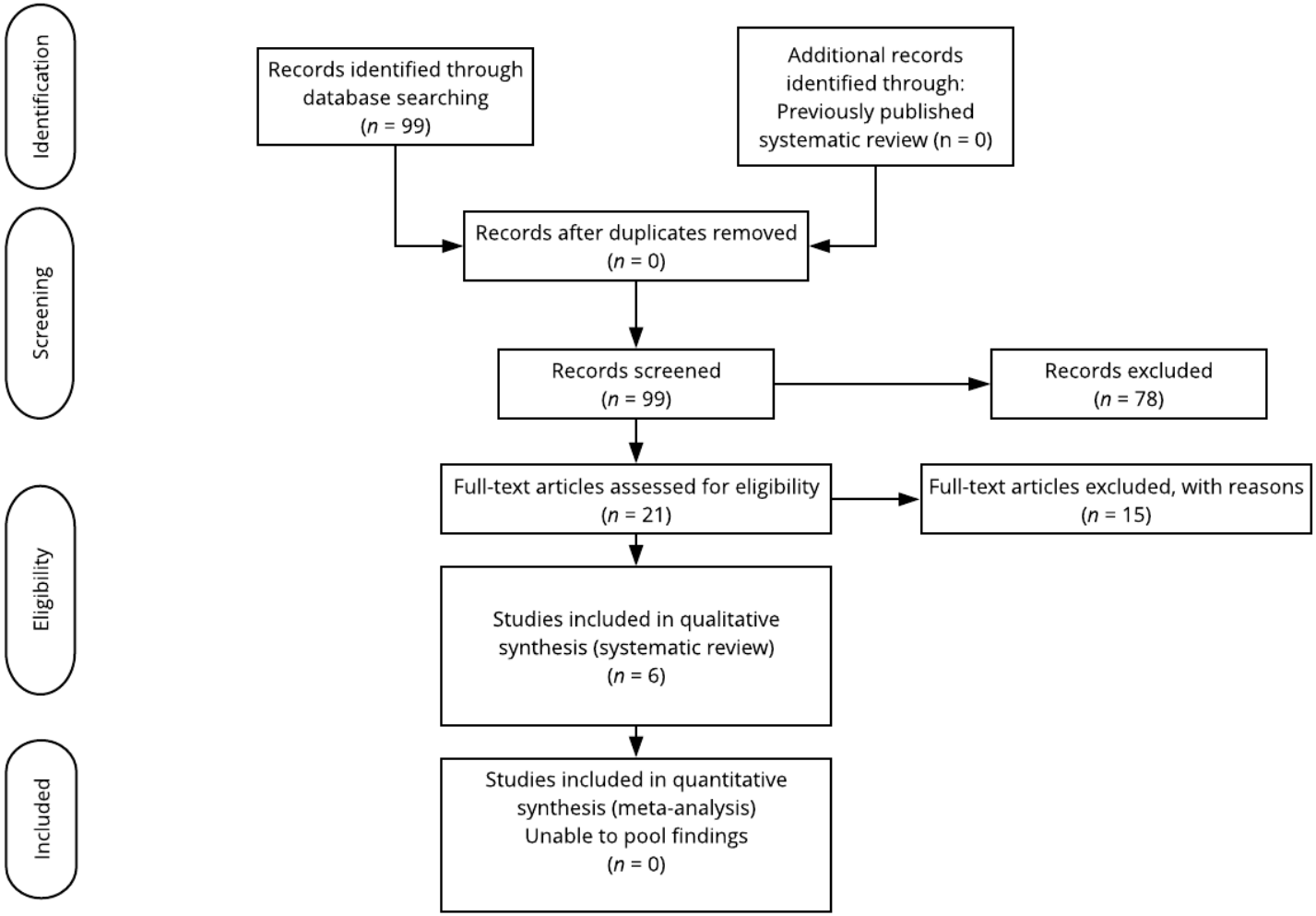

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRIMSA)[e]

Table 1
AGREE II$_d$ Summary for the ASCO Guideline (Hesketh et al., 2017)

Domain	Percent Agreement
Scope and purpose	97%
Stakeholder involvement	81%
Rigor of development	90%
Clarity and presentation	92%
Applicability	58%
Editorial independence	83%
Overall guideline assessment	6
Team's recommendation for guideline use	Yes

Note: Four EBP Team members or Scholars completed the AGREE II on this guideline.

Table 2
AGREE II$_d$ Summary for the MASCC Guideline (Dupuis et al., 2017)

Domain	Percent Agreement
Scope and purpose	93%
Stakeholder involvement	51%
Rigor of development	69%
Clarity and presentation	61%
Applicability	19%
Editorial independence	94%
Overall guideline assessment	5
Team's recommendation for guideline use	Yes

Note: Four EBP Team members or Scholars completed the AGREE II on this guideline.

Characteristics of Intervention Studies

Dubinski et al. (2018)

Characteristics of Study	
Methods	**Retrospective Cohort**
Participants	**Participants**: Adults with newly diagnosed GBM **Setting:** University Hospital in Helsinki **Number enrolled into study:** *N* = 113 **Gender, males: (as defined by researchers)** • *n* = 59 (52%) **Race / ethnicity or nationality (as defined by researchers):** • The study occurred in Helsinki, Finland. The authors did not identify race or ethnicity of the participants. **Age, years, standard deviation** • 58 (12.72) **Inclusion criteria:** • Patients admitted to the hospital who were newly diagnosed with GBM • Underwent craniotomy from 2011 to 2013 **Exclusion criteria:** • Patients with pre-existing disease likely to impact their immune status (bacterial infection, fewer, congenital or acquired immunodeficiency, autoimmune disease, or current immunotherapy) • Patients detailed DEX intake was not reported. **Covariates identified:** • Not reported
Interventions	• Symptomatic patients whose condition was attributed to peritumoral edema received 12 mg DEX per day. • DEX was administrated until craniotomy, which was performed within 4 ± 1 day after admission. • All patients received 40 mg DEX during the perioperative period to reduce surgically induced cerebral edema.
Outcomes	**Primary outcome(s):** • To correlate the initial DEX response with patient's survival and to analyze its effect on tumor leukocyte infiltration in newly diagnosed glioblastoma (GBM) patients. • Disease progression was diagnosed in case of either new gadolinium enhancement, T2 FLAIR progression, worsening of neurologic symptoms or death. OS was defined as the time interval between diagnosis and death.
Results	**Results:** • Patient age was identified to be a risk factor for the development of dexamethasone- induced leukocytosis, median = 63 years, $p < .05$. • The presence of dexamethasone-induced leukocytosis decreased overall survival, *HR* = 2.25, 95% CI [1.15, 4.38]; p < .001. • The presence of dexamethasone-induced leukocytosis decreased progression-free survival, *HR* = 2.23, 95% CI [1.09, 4.59]; $p < .01$. **Limitations:** • Analysis was retrospective • Several patients were excluded due to the lack of detailed DEX intake data, making a selection bias possible.

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Hui et al. (2019)

Characteristics of Study

Methods	**Retrospective cohort**

Participants	**Participants:** Adults newly diagnosed with nonmetastatic GBM who received standard photon radiotherapy with concurrent chemotherapy
	Setting: Washington University Medical Center, St. Louis, MO
	Number enrolled into study: *N* = 319
	• **Group 1,** Low-dose corticosteroid (≤ 2 mg/day)**:** *n* = 170
	• **Group 2,** High-dose corticosteroid (>2 mg/day)**:** *n* = 149
	Number completed: *N* = 319
	Gender, males: (as defined by researchers)
	• **Group 1:** *n* = 106 (62%)
	• **Group 2:** *n* = 88 (59%)
	Race / ethnicity or nationality (as defined by researchers):
	• **Group 1:**
	  • **White:** *n* = 159 (94%)
	  • **Other:** *n* = 11 (6%)
	• **Group 2:**
	  • **White:** *n* = 140 (94%)
	  • **Other:** *n* = 9 (6%)
	Age, median in years (range)
	• **Group 1:** 57 (22-82)
	• **Group 2:** 57 (21-78)
	Inclusion criteria:
	• Patients newly diagnosed with nonmetastatic GBM
	• Patients that:
	  ○ Received standard photon radiotherapy with concurrent chemotherapy
	  ○ Had an absolute lymphocyte count drawn at baseline (prior to radiation therapy) and within 3 months after starting radiation therapy
	  ○ Corticosteroid use at baseline and during chemoradiotherapy
	Exclusion criteria:
	• Patients treated with proton radiation therapy for resected GBM < 5 cm
	Covariates identified:
	• Gross-total resection (GTR)

Interventions	**Both:**
	• Radiation therapy was delivered by either:
	  ○ 3D conformal technique
	  ○ Intensity modulated photon-based technique
	• A cumulative dexamethasone dose was calculated by recording the dose recorded at four timepoints:
	  ○ Baseline (within two weeks of radiation therapy)
	  ○ Week 2 (± 1 week)
	  ○ Week 4 (± 1 week)
	  ○ Week 6 (± 1 week)

Outcomes	**Primary outcomes:** • Acute severe lymphopenia (ASL) defined as occurrence of ALC < 500 cells/mL within three months of starting RT • Overall survival (OS)* • Progression-free survival (PFS) **Secondary outcomes:** • Subgroup analysis of GTR group *Outcomes of interest to the CMH CPG or CAT development team

Results	Univariate analysis: • ASL High-dose corticosteroid cohort had significantly higher ASL rates (43.7%) compared to the low-dose cohort (19.8%) rates ($p < .001$) • OS (median follow up time of 14.6 months) High-dose corticosteroid cohort had significantly worse OS rates (12.6 months) compared to the low-dose cohort (17.9 months), $p < .001$ • PFS High-dose corticosteroid cohort (7.1 months) not significantly different compared to the low-dose cohort (8.1 months), $p = .163$ Multivariate analysis: • ASL ○ High-dose corticosteroid was independently associated with ASL OR = 1.283, 95% CIs [1.143, 1.441] ○ Average corticosteroid use was not significantly associated with ASL ○ **GTR subgroup analysis:** Higher average corticosteroids were not independently associated with ASL *OR* = 1.804, 95% CIs [1.345, 2.420] • OS ○ High-dose corticosteroid cohort was independently associated with OS *HR* = 1.131 95% CIs [1.059, 1.208] ○ Average corticosteroid use was not reported ○ Higher average corticosteroid was not independently associated with OS • PFS ○ High-dose corticosteroid cohort (7.1 months) not significant ○ Average corticosteroid use was not significantly associated with PFS ○ Higher average corticosteroid was not independently associated with PFS

Shields et al. (2015)

Characteristics of Study	
Methods	**Retrospective cohort**
Participants	**Participants:** Adults with GBM **Setting:** The Norton Cancer Institute, Louisville KY, USA **Number enrolled into study:** *N* = 73 **Primary analysis- (**did not answer the question asked and therefore those study findings are not included in this report) **Secondary analysis** • **Secondary Group 1:** Able to stop dexamethasone during radiation therapy: n = 36 • **Secondary Group 2**: Unable to stop dexamethasone during radiation therapy: n = 37 **Number completed:** *N* = 73 **Gender, males: (as defined by researchers)** • **Primary analysis: 44 (60%)** • **Secondary analysis:** Not reported **Race / ethnicity or nationality (as defined by researchers):** • The study occurred in Kentucky, USA. The authors did not identify race or ethnicity of the participants. **Age, median in years** • 61 **Inclusion criteria:** • Diagnosed with GBM multiforme • Treated with 30 fractions of simultaneous integrated boost radiation therapy, concurrent with BEV and TMZ, combined or TMZ alone **Exclusion criteria:** • None reported **Covariates identified:** • The cohort spans a time frame when the RTOG 0825 and AVAGlio studies were reported ○ Subjects prior to the reporting of the above studies received both BEV and TMZ ○ Subjects after the reporting of the above studies received BEV only.
Interventions	**Both:** • All subjects underwent surgical resection of the GBM, and extent of resection was determined by MRI. • All subjects received radiation therapy, of 30 identical fractions delivered once daily five times per week, for 6 weeks. • All subjects received DEX after surgical resection to manage intracranial edema, and to control neurological symptoms. The goal was to wean DEX prior to starting radiation therapy. **Dose not reported.** **Group 1:** • Subjects received TMZ (75 mg/m$_2$) daily, and BEV (10 mg/kg) every two weeks during 6 weeks of radiation therapy. One month after radiation therapy, TMZ (150 mg/m$_2$ for 5 days, monthly and BEV 10 mg/kg every two weeks until progression, toxicities, or 12 months total. **Group 2:** • Subjects received TMZ (75 mg/m$_2$) daily during 6 weeks of radiation therapy. One month after radiation therapy TMZ (150 mg/m2 for 5 days, monthly for up to one year. If salvage therapy was needed, subjects were offered BEV infusion every three weeks (*n* = 19 in this group who required salvage therapy) **Secondary analysis:** • **Group 1:** Patients who weaned from DEX prior to radiation therapy • **Group 2:** Patients who continued to receive DEX during radiation therapy

Outcomes	**Primary outcomes of secondary analysis:** • *Progression free time (PFS)- interval between diagnosis and progression • *Overall survival time (OS)- interval between diagnosis and death from any cause **Secondary outcome(s)** • Not reported **Safety outcome(s):** • Not reported *Outcomes of interest to the CMH CPG or CAT development team

Results	**Results:**
	• Overall
	• Progression free time, median
	  ○ DEX weaned – 8.8 months
	  ○ DEX not weaned - 6 months
	  ○ p = .002
	• Overall survival, median
	  ○ DEX weaned – 22.5 months
	  ○ DEX not weaned - 12.7
	  ○ p = .02

Wolff et al. (1998)

Characteristics of Study	
Methods	**Retrospective cohort**
Participants	**Participants:** Children **Setting:** Children's Hospital, Canada **Number enrolled into study:** *N* = 20, who underwent 57 courses of chemotherapy • **Group 1,** Courses with methotrexate alone (MTX)**:** *n* = 24 • **Group 2,** Courses with MTX and DEX**:** *n* = 33 **Number completed:** *N* = 20, who underwent 57 courses • **Group 1,** Courses with MTX alone**:** *n* = 24 • **Group 2,** Courses with MTX and DEX: *n* = 33 **Gender, males: (as defined by researchers)** • **Group 1:** Subjects *n* =4/8 received MTX and DEX (50%) • **Group 2:** Subjects *n* = 9/12 received MTX and DEX *(*75%) **Race / ethnicity or nationality (as defined by researchers):** The study occurred in Germany. The authors did not identify race or ethnicity of the participants. **Age, years, mean (range)** • **Group 1:** received MTX alone, 4.6 (1 to 15) • **Group 2:** received MTX and DEX. 4.6 (1 to 7) **Inclusion criteria:** • Brain tumor • Treated with MTX or MTX with DEX **Exclusion criteria:** • None stated **Covariates identified:** Not reported
Interventions	• **Group 1:** Treated with MTX alone • **Group 2:** Treated with MTX and DEX.
Outcomes	**Primary outcome:** • *Survival **Secondary outcome** • *Disease progression **Safety outcome(s):** • Not reported *Outcomes of interest to the CMH CPG or CAT development team
Results	**Results:** • There were no therapy related deaths in either group during chemotherapy • Disease progression is not reported • Hepatotoxicity was worse in the DEX group. Only *p* values are reported. ○ GOT and GPT maximal values were higher in those who received DEX, $p < .001$. ○ GOT and GPT increases were higher in those who received DEX, $p < .01$

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If you have questions regarding this CAT – please contact jcthompson@cmh.edu

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