Pneumocystis jirovecii pneumonia prophylaxis in patients with glioma receiving concurrent chemoradiation: a systematic review and meta-analysis

Jason L. Jia,[a,b,m] Bader Alshamsan,[c,m] Ana Beltran-Bless,[a,d,l] Megan MacRae,[e] Foster Rose,[a] Jennifer Leigh,[f,g] Deepro Chowdhury,[h] Francesco Fazzari,[i] Victor Lo,[a] Shing Fung Lee,[j,k] and Terry L. Ng[a,d,l,*]

[a]Department of Medicine, The Ottawa Hospital Cancer Centre, Ottawa, ON, Canada
[b]Department of Medicine, St. Joseph's Health Centre, Toronto, ON, Canada
[c]Department of Medicine, College of Medicine, Qassim University, Buraydah, Saudi Arabia
[d]Division of Medical Oncology, Department of Medicine, University of Ottawa, ON, Canada
[e]Queen's University Faculty of Medicine, Kingston, ON, Canada
[f]Division of Medical Oncology and Hematology, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada
[g]Department of Medicine, University of Toronto, Toronto, Ontario, Canada
[h]Division of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada
[i]University of Ottawa Faculty of Medicine, Ottawa, ON, Canada
[j]Department of Radiation Oncology, National University Cancer Institute, National University Hospital, Singapore
[k]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[l]Cancer Research Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada

eClinicalMedicine
2026;91: 103715
Published Online 27 December 2025
https://doi.org/10.1016/j.eclinm.2025.103715

Summary

Background Routine antibiotic prophylaxis against *pneumocystis jirovecii* pneumonia (PJP) is recommended during concurrent temozolomide and radiotherapy (TMZ-RT) for glioma based on early small studies. However, true PJP risk may be far lower, raising questions about the value and harms of universal prophylaxis.

Methods We conducted a systematic review (PROSPERO: CRD42021292396) of studies reporting PJP incidence among glioma patients treated with TMZ-RT. MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials were searched from inception to May 1, 2025. Outcomes included overall PJP incidence and rates stratified by prophylaxis, corticosteroid exposure, and lymphopenia.

Findings Of 3791 records, 35 studies (13,637 patients, 12,301 received TMZ-RT) met eligibility criteria. Across 24 studies confirming PJP, 71 cases occurred among 12,056 TMZ-RT patients—a pooled incidence of 0.74% (95% CI, 0.59–0.93%) with minimal heterogeneity (Q = 23.3, p = 0.44; I^2 = 1.4%). Seventeen studies detailed prophylaxis: 55.1% (2942/5341) of patients received it; PJP incidence was 0.8% (14/1765) with versus 0.3% (9/2719) without prophylaxis. Baseline corticosteroid exposure was reported in 13 studies (n = 5908: median 49.5%, range 27.3%–82.3%), and grade 3–4 lymphopenia in 15.2% (319/2102) of TMZ-RT patients. Incomplete study-level reporting precluded robust risk factor-adjusted analyses.

Interpretation Across heterogeneous populations and study designs, the pooled PJP incidence associated with TMZ-RT was 0.74% (95% CI, 0.59–0.93%). Due to the heterogeneity in study populations and designs, lack of standardized diagnostic confirmation, and incomplete reporting of steroid administration, this finding should be interpreted with caution. Currently available evidence suggests the risk of PJP is lower than the commonly cited 3.5% threshold for prophylaxis. Well-designed prospective studies are needed to clarify true infection risk and inform prophylaxis decisions.

Funding The Deanship of Graduate Studies and Scientific Research at Qassim University provided financial support for the article processing charge (APC) of this manuscript.

*Corresponding author. 501 Smyth Road, Division of Medical Oncology, Department of Medicine, University of Ottawa, Ottawa, ON, K1H 8L6, Canada.
E-mail address: teng@toh.ca (T.L. Ng).
[m]These authors contributed equally to this work
Jason L. Jia and Bader Alshamsan as co-first authors.

Keywords: Glioma; Brain cancer; Temozolomide; Pneumocystis jirovecii pneumonia; Antibiotic prophylaxis

Research in context

Evidence before this study

Antibiotic prophylaxis against *pneumocystis jirovecii* pneumonia (PJP) during glioma treatment was prompted by the pivotal phase II clinical trial of temozolomide plus radiotherapy (TMZ-RT) in which two PJP cases occurred among the first 15 patients. The subsequent phase III EORTC 22981/26,981/NCIC CE.3 trial which established the survival benefit of TMZ-RT mandated routine PJP prophylaxis. Subsequent cohort studies have reported much lower PJP rates, questioning the need for universal prophylaxis.

Added value of this study

This systematic review and meta-analysis summarizes data from over 13,000 glioma patients treated with TMZ-RT to explore the real-world risk of PJP and reports a pooled incidence of 0.74%. While guideline recommendations support prophylaxis, many patients were not given preventive treatment. The available evidence suggests the risk may be lower than the commonly cited 3.5% threshold, but this remains uncertain.

Implications of all the available evidence

Current evidence indicates that the risk of PJP during and after TMZ-RT appears low, though limitations in the data prevent firm conclusions. While routine prophylaxis for all glioma patients may not be clearly justified based on existing evidence, decisions should be individualized, considering patient-specific risk factors and acknowledging the need for further high-quality studies.

Introduction

Pneumocystis jirovecii is an opportunistic fungal species that can cause the syndrome of *pneumocystis jirovecii* pneumonia (PJP) in immunocompromised individuals. PJP is characterized by dyspnea, cough, and interstitial pulmonary infiltrates, and may progress to fulminant respiratory failure. *Pneumocystis jirovecii* asymptomatically colonizes 20% of healthy adults,[1] but it can cause lethal, tissue-invasive disease in susceptible patients.[2,3] The risk of PJP is particularly well known amongst patients with human immunodeficiency virus (HIV) with low CD4 T lymphocyte counts. PJP in non-HIV patients has a characteristically more aggressive disease course and is most prevalent in patients undergoing hematologic malignancy treatment.[4,5] The risk of infection varies by intensity of concurrent chemotherapy treatment and ranges from two to 22%.[5] For such patients, antibiotic prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) is routinely recommended to reduce PJP incidence and mortality.[2]

The evidence supporting routine PJP prophylaxis during the treatment of glioblastoma multiforme (GBM) and lower grade gliomas with temozolomide (TMZ) given concurrently with radiotherapy (TMZ-RT) is limited. In the landmark phase II trial of concurrent and adjuvant TMZ-RT, two severe PJP cases occurred amongst the first 15 patients who did not receive PJP prophylaxis.[6] As a result, antibiotic prophylaxis became mandatory and was routinely implemented in subsequent clinical trials that utilized TMZ-RT. Regulatory agencies, including the U.S. Food and Drug Administration (FDA), Health Canada, and Cancer Care Ontario (CCO), specify in their TMZ product monographs that PJP prophylaxis is required for all patients receiving TMZ-RT.[7–9] The only major guideline to qualify this recommendation is from the National Comprehensive Cancer Network (NCCN), which advises prophylaxis during TMZ-RT and until lymphocyte recovery.[10] The American Society of Clinical Oncology (ASCO) does not instruct on prophylaxis during TMZ-RT specifically, but does recommend its use for patients receiving chemotherapy regimens associated with greater than 3.5% PJP risk.[11] The European Society for Medical Oncology (ESMO) similarly recommends prophylaxis in patients undergoing TMZ-RT.[12]

TMZ-RT followed by adjuvant TMZ remains a standard frontline treatment of both high- and low-grade gliomas.[8] Based on formal recommendations, PJP prophylaxis is required in all cases. However, the possible toxicities of TMP-SMX, the most common prophylactic antibiotic for this indication, include severe and possibly life-threatening dermatologic eruptions, blood dyscrasias, kidney injury.[13]

A meta-analysis of 12 trials of PJP prophylaxis determined the rate of severe adverse effects to be 3.1%.[2] Therefore, PJP prophylaxis with TMP-SMX would only be recommended if the risk of PJP infection exceeded 3.5%. There is no randomized controlled trial data reporting PJP risk amongst patients receiving TMZ-RT with and without prophylaxis. Most real-world reports on PJP risk are based on cohort studies. Furthermore, only 70% of oncologists in the US and 42% of oncologists in Canada routinely prescribe PJP prophylaxis.[14,15]

The primary objective of this systematic review was to identify and consolidate relevant clinical reports of PJP in glioma patients treated with TMZ-RT to estimate real-world PJP incidence rates.

Methods

Research question and study eligibility criteria

We conducted a systematic literature review to address the questions: "What is the risk of PJP in glioma patients receiving TMZ-RT?" and "What is the current evidence guiding the management of PJP risk in this population?". The review was reported in accordance with Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[16] The initial protocol was registered to the PROSPERO database (CRD42021292396).

We used the Population-Intervention-Comparator-Outcomes framework to organize the review. The population included patients aged ≥18 years with histologically-confirmed glioma including diffuse oligodendroglioma (DO), diffuse astrocytoma (DA), anaplastic oligodendroglioma (AO), anaplastic astrocytoma (AA), GBM, and IDH-mut grade 4 astrocytoma treated with TMZ-RT. The primary outcome was PJP incidence among patients treated with TMZ-RT, overall and in prophylaxis usage subgroups. Secondary outcomes included PJP incidence according to corticosteroid exposure and lymphopenia, and patterns of prophylactic antibiotic selection.

Search strategy and study selection

A research specialist (R.S.) designed and executed the electronic literature search in MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. The search strategy (Appendix 1) encompassed MeSH and free text words "glioma", "oligodendroglioma", "astrocytoma", "oligoastrocytoma", "glioblastoma", "temozolomide", and their derivatives from 1946 to February 1, 2022. Two updated searches using the same search strategy were completed on January 1, 2024, and May 1, 2025, respectively. Eligible studies included randomized clinical trials and cohort studies involving at least 30 patients. Non-English publications, case reports, commentaries, and editorials were excluded.

Publications were screened in two stages by two independent reviewers. During stage 1, studies were selected based on title and abstract. In stage 2, subsequent publications underwent full-text review. Disagreements were adjudicated by a third team member (T.L.N.).

Data abstraction and risk of bias assessment

All eligible publications were abstracted for prespecified study characteristics, patient cohort information and study outcomes using a standardized abstraction form. Study characteristics included primary author, year of publication, design, countries of involvement, dates of study enrollment and follow-up, and study objectives. Patient information included pathologic diagnosis (including WHO classification) and cancer treatments received (including proportion of the study cohort receiving TMZ-RT). Key study outcomes included total number of PJP cases, number of PJP cases with and without concurrent TMZ-RT, number of PJP cases with and without PJP prophylaxis, number of PJP cases associated by lymphopenia, lymphopenia severity, and corticosteroid usage at time of PJP diagnosis and at baseline. Baseline referred to the time point when starting assigned treatment. Data on the types of PJP prophylaxis used and the number of pneumonia cases not otherwise specified were also collected.

Risk-of-bias for prospective studies was assessed using the Cochrane Collaboration's Risk of Bias Tool 2.[17] A study was categorized as high risk-of-bias if one or more of five domains of bias was deemed high risk. For retrospective studies, risk-of-bias was assessed using a modified Newcastle–Ottawa Scale (NOS).[18] The overall study quality regarding the outcome of PJP incidence was categorized as good, moderate, or poor based on the number of criteria fulfilled.

Statistics

For each study, the number of PJP cases and the total number of patients were entered into Comprehensive Meta-Analysis (CMA, version 4). CMA calculated study-specific incidence (the proportion of patients with PJP) and pooled them using random-effects models with the DerSimonian-Laird estimator. Independent replication and figure production (forest and funnel plots) were performed in R (version 4.5.1) using the meta package. The primary analysis applied a random-effects model with logit transformation, which stabilizes within-study variance and accommodates rare events. To assess robustness, sensitivity analyses were conducted using the Freeman-Tukey double arcsine (PFT) transformation and raw proportions. Alternative model specifications were examined, including fixed-effects models and random-effects models with the Hartung-Knapp adjustment, which provides more conservative confidence intervals.

Between-study heterogeneity was quantified using the Q statistic, τ^2, and I^2 with 95% confidence intervals. Prediction intervals were calculated to describe the expected range of incidence rates in future studies. Potential small-study effects and publication bias were evaluated visually using funnel plots and formally using Egger's regression test. Duval and Tweedie's trim-and-fill method was applied to estimate the potential influence of unpublished studies on the pooled effect.

Ethics

As this systematic review and meta-analysis was conducted using data from previously published studies, and confidential data was not involved, informed consent and ethical approval were not required.

Role of funding source

The Deanship of Graduate Studies and Scientific Research at Qassim University provided financial

support solely for the article processing charge (APC) of this study. The funding body had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to the data and take full responsibility for the integrity and accuracy of the analysis. There are no other funding sources to disclose.

Results

Study characteristics

The initial systematic search up to February 2022 identified 2549 citations. In stage 1 screening, 1843 citations were excluded. In stage 2 screening, 685 studies were excluded. The remaining 21 publications were included for data abstraction.[6,19–38] An additional systematic search to January 2024 identified 454 further citations. In stage 1 screening, 308 publications were excluded. In stage 2 screening, 139 studies were excluded. The remaining 7 were included in the final analysis.[39–45] A third search up to May 1, 2025 identified 788 citations. In stage 1 screening, 704 studies were excluded. In stage 2 screening, 77 were excluded. The remaining 7 were included in the final analysis.[46–52] In total, 35 publications fulfilled eligibility criteria (Fig. 1).

Included studies were published between 2002 and 2025. Fourteen involved the USA,[21,22,25,27,35–37,41,46–51] six with Canada,[29,33,42,43,46,47] and six with Italy.[20,34,38,44,46,47] Study designs included 20 prospective studies (seven randomized controlled trials[25,29,36,41,46–48] and 13 single-arm cohort studies[7,18,20,22,25,26,28,30,32,34,50–52]) and 15 retrospective cohort studies (five with comparator groups[20,29,38,42,43] and ten single cohort[21,24,30,32,33,35,37,44,45,49]). A primary outcome was defined in 21 publications including overall survival (OS) in 12 studies,[19,22,24,25,27,30,33,36,46–48] progression-free survival (PFS) in four studies,[24,26,30,40] and PJP diagnosis in two studies.[42,43] Secondary and unspecified outcomes included efficacy (28 studies), safety/toxicity (26 studies), and PJP incidence (one study) (Table 1).

Study risk of bias

Risk of bias assessments (Table 2) determined that all 20 prospective studies demonstrated high overall risk primarily due to lack of randomization of PJP prophylaxis. Of the retrospective studies, 14 of 15 were considered poor quality, commonly from lack of reporting on the method of PJP diagnosis. One publication was considered high quality based on its usage and reporting of validated PJP diagnostic methods amongst a comprehensive population of high-grade glioma patients.[37]

Patient characteristics

The 35 publications included a total of 13,637 patients (range, 33 to 5130 per study). Brain cancer diagnoses were specified for 8328 patients (GBM n = 6,999, AA n = 489, AO n = 251, DA n = 168, DO n = 79, astrocytoma grade 4 n = 288, gliosarcoma n = 18) and were missing or unspecified for 5294 patients. WHO classification systems varied across studies due to evolving diagnostic criteria.[53–57] Twenty-five studies did not report which WHO classification system was used, whereas ten studies did (1993 n = 1, 2000 n = 2, 2002 n = 1, 2007 n = 2, 2016 n = 2, 2021 n = 2).

In total, 12,301 of 13,637 patients (90.2%) received TMZ-RT. The remaining 1336 patients belonged to comparator cohorts: 603 (4.4%) TMZ-RT with an investigational agent, 75 (0.5%) TMZ after RT, 462 (3.3%) RT alone, 128 (0.9%) TMZ alone, 43 (0.3%) best-supportive care, and 25 (0.2%) with unknown post-operative management. Table 3 summarizes study

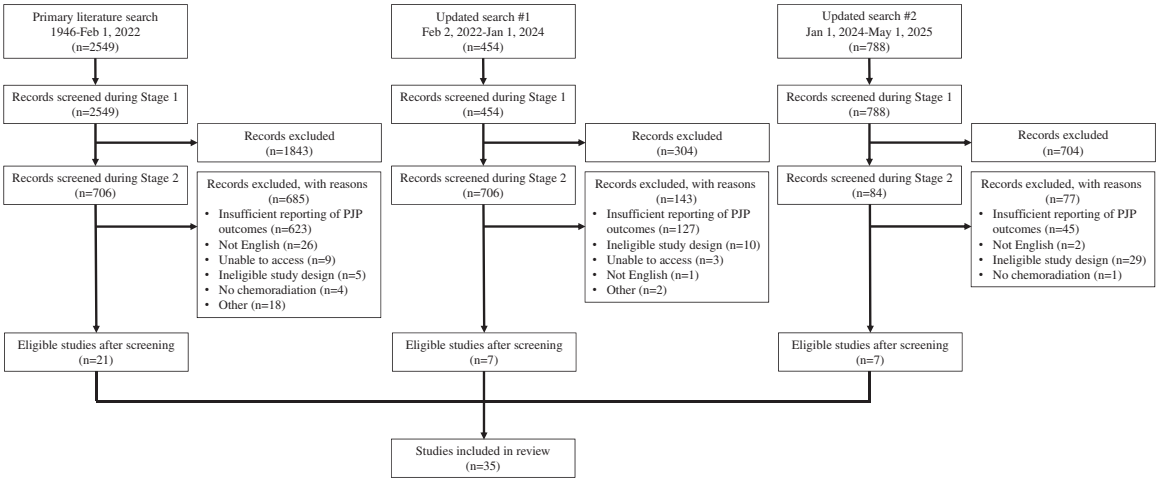

Fig. 1: PRISMA flow diagram outlining the study eligibility screening process across three separate literature searches of studies on *pneumocystis jirovecii* pneumonia (PJP) in glioma patients receiving concurrent chemoradiation.

Study	Design	Country	Dates of patient enrollment	Study aim	Primary outcome(s)	Other outcome(s)
Stupp, 2002[6]	Phase II	Switzerland	NR	Evaluate concurrent TMZ with RT and adjuvant TMZ.	Safety, tolerability	OS
Stupp, 2005[19]	Phase III	15 countries	2000–2002	Randomize and compare concurrent TMZ with RT followed by adjuvant TMZ to RT alone.	OS	PFS, safety, QOL
Corsa, 2006[20]	Retrospective chart review	Italy	1997–2001	Compare outcomes of two cohorts, treated either with RT and adjuvant TMZ or with TMZ concurrent and adjuvant with RT.	OS	Toxicity
Gerber, 2007[21]	Retrospective chart review	USA	2004–2005	Evaluate myelosuppression with TMZ concurrent and adjuvant with RT.	Incidence of thrombocytopenia	Hematologic toxicity
Brown, 2008[22]	Phase I/II	USA	2004–2005	Evaluate combination of standard concurrent TMZ with RT and erlotinib.	MTD, OS	PFS
Dall'oglio, 2008[23]	Phase II	Italy	2005–2007	Evaluate dose-intense regimen of adjuvant TMZ following postoperative concurrent TMZ with RT.	Toxicity	OS
Yaman, 2008[24]	Retrospective chart review	Turkey	2005–2007	Evaluate TMZ administered concurrently with RT and as consolidation.	OS, PFS	Response, safety, prognostic factors
Clarke, 2009[25]	Phase II	USA	2005–2007	Randomize dose-dense and metronomic adjuvant TMZ after concurrent TMZ with RT, followed by 13-*cis*-retinoic acid and compare to historical controls.	OS	PFS, toxicity
Weiler, 2010[26]	Phase II	Germany	2005–2006	Evaluate intensified adjuvant TMZ schedule before and after concurrent TMZ with RT, alongside indomethacin.	PFS	PFS, OS, remission rate, toxicity
Grossman, 2011[27]	Prospective cohort	USA	2004–2008	Follow patients with HGG receiving RT, TMZ, glucocorticoids and identify patterns of immunosuppression and complications including infection.	CD4 toxicity	Infection, hospitalization, OS
Kim, 2011[28]	Prospective	Seoul	2003–2008	Evaluate concurrent TMZ with RT followed by adjuvant TMZ for WHO grade III gliomas.	OS	PFS, KPS, toxicity
Cao, 2011[29]	Retrospective chart review	Canada	2000–2009	Compare upfront concurrent TMZ and hypofractionated RT to RT alone with salvage TMZ.	OS	PFS, toxicity
Demirici, 2011[30]	Retrospective chart review	Turkey	2005–2010	Presentation of long-term experience with CCRT with TMZ followed by maintenance TMZ.	PFS, OS	Toxicity
Iliadis, 2012[31]	Prospective	Greece	2005–2007	Explore significance of volumetric MR data in prognostic categorization in patients treated with postoperative RT and TMZ.	PFS, OS	MGMT correlation
Malkoun, 2012[32]	Retrospective chart review	France	2006–2008	Evaluate prolonged maintenance TMZ after initial CCRT with TMZ.	Feasibility, and efficacy (OS, PFS)	Prognostic factors
Pitz, 2012[33]	Retrospective cohort	Canada	2002–2008	Evaluate extended duration TMZ and *cis*-retinoic acid following CCR with TMZ.	OS	PFS, toxicity
Salmaggi, 2013[34]	Phase II	Italy	NR	Evaluate carmustine wafers with CCRT with TMZ.	RFS	OS, toxicity
Tanaka, 2013[35]	Retrospective chart review	USA	2003–2008	Review outcomes and treatment patterns including CCRT of elderly patients.	OS	PFS, toxicity
Clarke, 2014[36]	Randomized trial	USA	2007–2008	Evaluate CCRT with TMZ, in addition to erlotinib and bevacizumab.	OS	PFS, safety
Neuwelt, 2014[37]	Retrospective chart review	USA	1999–2012	Evaluate PJP outcomes with adjuvant CCRT with TMZ and maintenance TMZ.	PJP incidence	Treatment-related risk factors
Parisi, 2015[38]	Retrospective analysis	Italy	1994–1996	Compare adjuvant RT to adjuvant CCRT with TMZ.	OS	PFS, prognostic factors, hematologic toxicity
Saran, 2021[39]	Phase I	UK	2009–2012	Define the toxicity and dose of afatinib in combination with RT.	MTD	Toxicity, ORR, pharmacokinetics
Lim, 2022[40]	Phase III	19 countries	2016–2019	Randomize and compare concurrent TMZ and RT with nivolumab versus placebo.	PFS, OS	Safety
Peters, 2022[41]	Randomized trial	USA	2011–2013	Randomize patients receiving CCRT with TMZ and RT to low-dose naltrexone or placebo to determine impact on QOL.	Patient-reported QOL	Patient-reported fatigue, adverse effects
Climans, 2022[42]	Retrospective cohort	Canada	2005–2019	Identify and compare clinical features of patients who developed PJP during concurrent TMZ and RT with those who did not develop PJP.	PJP diagnosis	Lymphocyte count, explanatory variables
Climans, 2022[43]	Retrospective cohort	Canada	2005–2019	Determine the risk of PJP during TMZ CCRT with and without antibiotic prophylaxis.	Risk of PJP	OS, rate of hospitalization, rate of neutropenia
Bruno, 2022[44]	Retrospective case series	Italy	2015–2020	Investigate the impact of surgery and adjuvant treatment on survival including identification of relevant prognostic factors particularly amongst elderly patients.	PFS, OS	Toxicity, prognostic factors
Demircan, 2023[45]	Retrospective chart review	Turkey	2009–2019	Identify significant prognostic factors towards survival, including the effects of lymphopenia and the importance of RT timing.	OS	PFS, toxicity, prognostic factors

(Table 1 continues on next page)

Study	Design	Country	Dates of patient enrollment	Study aim	Primary outcome(s)	Other outcome(s)
(Continued from previous page)						
Omuro, 2022[46]	Phase III	19 countries	2016–2018	Randomize and compare concurrent TMZ and RT with nivolumab and RT.	OS	PFS, safety and tolerability, health-related quality of life
Lassman, 2022[47]	Phase III	26 countries	2015–2018	Randomize and compare concurrent TMZ and RT and depatux-m with TMZ and RT and placebo.	OS	PFS, molecular subgroup analyses, neurocognitive function, patient-reported outcomes
Sim, 2022[48]	Phase II	Australia, USA	2018–2021	Randomize and compare maintenance nivolumab and TMZ with standard TMZ post concurrent TMZ and RT.	OS	PFS, toxicity, HR-QOL, neurologic function
Arnold, 2024[49]	Retrospective chart review	USA	2014–2021	Evaluate the frequency of hematologic toxicity during chemoradiation amongst patients receiving PJP prophylaxis.	Risk of hematological toxicity by PJP prophylaxis type	Severity of toxicity, influencing factors
Sloan, 2024[50]	Phase I	USA	2015–2017	Determine the maximum safe dose of ipilimumab and/or nivolumab given with maintenance TMZ.	DLT	Adverse effects, OS
Goldlust, 2024[51]	Phase I	USA	2017–2020	Evaluate the safety and tolerability of combined RT + TMZ and Novo-TTF-200 A device.	Adverse effects	OS, PFS, QOL
Narang, 2025[52]	Prospective cohort	India	2010–2018	Analyze long-term outcomes for patients diagnosed with astrocytoma grade 4 treated with TMZ + RT and adjuvant TMZ.	OS	PFS, prognostic factors, toxicity

List of studies fulfilling eligibility criteria and abstracted listed by date of publication, including study design, location, time span, aim, primary outcome(s), and other outcome(s). NR: not reported; TMZ: temozolomide; RT: radiation therapy; CCRT: concurrent chemoradiation; HGG: high-grade glioma; GBM: glioblastoma multiforme; OS: overall survival; PFS: progression free survival; QOL: quality of life; HR-QOL: health-related quality of life; MTD: maximum tolerated dose; DLT: dose-limiting toxicity; KPS: Karnofsky performance scale; ORR: objective response rate; RFS: recurrence-free interval; PJP: *pneumocystis jirovecii* pneumonia.

Table 1: **Summary of studies included in systematic review.**

populations, cancer treatment interventions, usage of PJP prophylaxis, PJP risk factors (corticosteroid use and lymphopenia), and PJP outcomes.

PJP prophylaxis and infection outcomes

Seventeen studies reported prophylaxis use. It was routine for all TMZ-RT patients in seven studies,[19,26,29,34,40,47,52] partial in three studies,[6,43,49] and absent in one study.[37] Five studies recommended prophylaxis but gave no details.[21,22,27,28,36] Among the 11 studies providing explicit data on prophylaxis administration, 2942 of 5341 TMZ-RT patients (55.1%) received prophylaxis: TMP-SMX was used in six studies, pentamidine in three studies, dapsone in two studies, and co-trimoxazole in one study. Studies that only "recommended" prophylaxis did not report type and duration.

PJP infection was explicitly reported in 24 of 35 (68.6%) studies. Fourteen of these 24 reported at least one case,[6,19,22,23,26,27,31,32,35,37,40,42,43,45] totaling 71 cases (study level PJP: 1 to 38 cases) among 10,589 TMZ-RT patients, and ten studies confirmed no PJP events in 1467 patients. The other 11 of 35 studies (34.3%) lacked direct case reporting but were retained to avoid underestimating risk.[21,29,36,39,41,44,47,48,50–52] Seven of these 11 studies reported a combined 7 cases of non-specific pneumonia in 484 patients.[29,36,39,41,48,50,51]

Two Canadian Institute for Clinical Evaluative Studies (ICES) retrospective cohorts accounted for the highest PJP incidence.[32,42] The first documented 38 cases among 5130 TMZ-RT patients (0.7%); 71% occurred within 90 days of starting RT and 29% within 91–365 days; prophylaxis use was not reported.[41] The second publication documented 18 cases among 3225 TMZ-RT patients (0.6%)[43]; prophylaxis was given to 648 patients (20.1%), and 12 of 18 infections occurred despite prophylaxis.

Excluding these ICES studies, the remaining 12 studies (n = 34 to 709) described 15 PJP cases among 2234 patients (0.67%). Of these, 1763 (78.9%) received TMZ-RT and 13 (0.74%) developed PJP. Infections occurred during chemoradiation (n = 7), maintenance TMZ (n = 1), post-TMZ-RT without maintenance (n = 1), or at an unknown time point (n = 4). No cases occurred among patients documented as receiving prophylaxis; five arose in patients without prophylaxis, and eight where prophylaxis status was unknown. Among the 521 patients who did not receive TMZ-RT, two PJP cases were reported (both RT-only). Clinical outcomes of PJP infection included hospitalization with recovery (n = 4), death (n = 4), and not reported (n = 7).

Ten studies reported PJP as a clinical outcome and documented zero cases.[20,24,25,28,30,33,34,38,46,49] Together, these included 1068 TMZ-RT-treated patients. One study mandated PJP prophylaxis for all 35 TMZ-RT patients,[34] one study reported prophylaxis usage for 214 of 217 (98.6%) patients,[49] one study recommended prophylaxis without confirming adherence,[28] and seven did not report prophylaxis practices.

Cochrane Risk of Bias Tool 2

Study	Risk of bias originating from:					Overall risk of bias judgement
	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of outcome	Selection of the reported outcome	
Stupp, 2002[6]	High	Low	Low	High	Low	**High**
Stupp, 2005[19]	Low	Low	Low	High	Low	**High**
Brown, 2008[22]	High	Some concerns	Low	High	Low	**High**
Dall'oglio, 2008[23]	High	Low	Low	High	Low	**High**
Clarke, 2009[25]	Some concerns	Low	Low	High	Low	**High**
Weiler, 2010[26]	High	High	Low	High	Low	**High**
Grossman, 2011[27]	High	Low	Low	High	Low	**High**
Kim, 2011[28]	High	High	Low	High	Low	**High**
Iliadis, 2012[31]	High	Low	Low	High	Low	**High**
Salmaggi, 2013[34]	High	Low	Low	High	High	**High**
Clarke, 2014[36]	High	Some concerns	Low	High	Some concerns	**High**
Saran, 2021[39]	High	Some concerns	High	High	Low	**High**
Lim, 2022[40]	Low	Low	Low	High	Low	**High**
Peters, 2022[41]	Low	Low	High	High	Low	**High**
Omuro, 2022[46]	Low	Low	Low	High	Low	**High**
Lassman, 2022[47]	Low	Low	High	High	Low	**High**
Sim, 2022[48]	Low	Low	High	High	Low	**High**
Sloan, 2024[50]	High	Low	High	High	Low	**High**
Goldlust, 2024[51]	High	Low	High	High	Low	**High**
Narang, 2025[52]	High	Low	High	High	Low	**High**

Modified Newcastle–Ottawa Scale

Study	Did the patient(s) represent the whole case(s) of the medical center?	Was the diagnosis correctly made?	Were other important diagnosis excluded?	Were all important data cited in the report?	Was the outcome correctly ascertained?	Overall quality of the report
Corsa, 2006[20]	Yes	Yes	Yes	No	No	**Poor**
Gerber, 2007[21]	Yes	Yes	Yes	No	No	**Poor**
Yaman, 2008[24]	Yes	Yes	Yes	No	No	**Poor**
Cao, 2011[29]	Yes	Yes	Yes	No	No	**Poor**
Demirici, 2011[30]	Yes	Yes	Yes	No	No	**Poor**
Malkoun, 2012[32]	Yes	Yes	Yes	No	No	**Poor**
Pitz, 2012[33]	Yes	Yes	Yes	No	No	**Poor**
Tanaka, 2013[35]	Yes	Yes	Yes	No	No	**Poor**
Neuwelt, 2014[37]	Yes	Yes	Yes	Yes	Yes	**Good**
Parisi, 2015[38]	Yes	Yes	Yes	No	No	**Poor**
Climans, 2022[42]	Yes	Yes	No	Yes	No	**Poor**
Climans, 2022[43]	Yes	Yes	No	Yes	No	**Poor**
Bruno, 2022[44]	Yes	Yes	Yes	No	No	**Poor**
Demircan, 2023[45]	Yes	Yes	No	No	No	**Poor**
Arnold, 2024[49]	Yes	Yes	No	No	No	**Poor**

List of studies fulfilling eligibility criteria with risk-of-bias assessments, separated by tool. The Cochrane Risk of Bias Tool 2 was applicable to prospective studies and the Modified Newcastle–Ottawa Scale was applicable to retrospective studies.

Table 2: **Risk of bias of included studies.**

Nine additional publications described pulmonary or infectious events where PJP was neither confirmed nor definitively excluded.[21,29,36,39,41,44,48,50,51] These involved 532 TMZ-RT patients. Reported events included: one case of drug or pneumocystis pneumonitis,[36] one case of unspecified pneumonitis,[50] three single cases of lung infection,[28,38,40,47,50] two postoperative systemic infections,[43] and one case of aspergillus pneumonitis.[21] Among these nine studies, one mandated PJP prophylaxis for all 57 TMZ-RT patients,[28] two studies recommended prophylaxis but did not confirm adherence,[21,36] and six did not describe prophylaxis.[39,41,44,48,50,51] A potential link between risk of PJP infection and prophylaxis could be inferred in only one instance: an

Study	Population	WHO	Intervention	PJP prophylaxis	PJP outcomes	Secondary outcomes
Stupp, 2002[6]	GBM (n = 62)	1993	62 received RT + TMZ, of which 49 proceeded to adjuvant TMZ.	No prophylaxis (n = 15) Pentamidine (n = 47)	Total cases of PJP (n = 2) Cases with CCRT (n = 2) Cases without CCRT (n = 0) Cases with prophylaxis (n = 0) Cases without prophylaxis (n = 2) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	Both patients hospitalized and survived. Lymphopenia grade 3/4 (n = 49, 80%) Steroids administered as needed; exact pattern not reported.
Stupp, 2005[19]	GBM (n = 573)	2000	573 enrolled. 287 received postsurgical experimental RT + TMZ, 286 received RT. Both groups subsequently planned to receive maintenance TMZ.	No prophylaxis (n = 0) Inhaled pentamidine or TMP-SMX (n = 573)	Total cases of PJP (n = 1) Cases with CCRT (n = 0) Cases without CCRT (n = 1) Cases with prophylaxis (n = 0) Cases without prophylaxis (n = 2) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 8)	Patient outcome not reported. Lymphopenia grade 3/4 (NR) Baseline steroid usage in 193 cases (67%) and 215 cases (75%) in RT + TMZ and RT alone groups respectively.
Corsa, 2006[20]	GBM (n = 43) AA (n = 21)	NR	64 received RT and TMZ. 33 treated with concurrent RT + TMZ and adjuvant TMZ, and 31 with RT followed by TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 0) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)
Gerber, 2007[21]	GBM (n = 38) AA (n = 11) AO (n = 3)	NR	52 received RT + TMZ followed by adjuvant TMZ.	No prophylaxis (NR) Prophylaxis (NR) Prophylaxis with TMP-SMX given to "almost all" patients	Total cases of PJP (NR) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (NR) "Most" patients received steroids.
Brown, 2008[22]	GBM (n = 97)	NR	97 received RT + TMZ preceded by and concurrent with experimental erlotinib, followed by maintenance TMZ and erlotinib.	No prophylaxis (NR) Prophylaxis (NR) Prophylaxis "strongly encouraged"	Total cases of PJP (n = 2) Cases with CCRT (n = 2) Cases without prophylaxis (n = 2) Cases with lymphopenia (n = 0) Cases with steroid (n = 2) Pneumonia not specified (NR)	Both patients died from PJP. Lymphopenia grade 3/4 (n = 11, 11.5%) Baseline steroid usage in 59 cases (61%).
Dall'oglio, 2008[23]	GBM (n = 32) AA (n = 2)	NR	34 received RT + TMZ followed by experimental maintenance TMZ in 1-week-on/1-week-off fashion	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 1) Cases with CCRT (NR) Cases without CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 1)	Patient hospitalized and recovered. 0 cases of grade 3/4 lymphopenia. 2 cases (6%) of grade 1 neutropenia. Steroids kept at lowest dosage per neurologic status.
Yaman, 2008[24]	GBM (n = 53) AA (n = 9)	2000	64 received RT + TMZ and adjuvant TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 0) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (NR) Dexamethasone used in 30 cases (48.4%) to control neurologic symptoms.
Clarke, 2009[25]	GBM (n = 85)	NR	85 started RT + TMZ, 59 of whom proceeded to maintenance TMZ in dose-dense or metronomic fashion and further 13-*cis*-retinoic acid.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 0) Pneumonia not specified (NR)	20 cases (23.5%) grade 3/4 lymphopenia during RT + TMZ. 3 (10%) and 1 (4%) during maintenance dose-dense and metronomic TMZ respectively. Steroid usage pattern not reported.

(Table 3 continues on next page)

Study	Population	WHO	Intervention	PJP prophylaxis	PJP outcomes	Secondary outcomes
(Continued from previous page)						
Weiler, 2010[26]	GBM (n = 39)	NR	39 started RT + TMZ, of whom 36 completed CCRT.	No prophylaxis (n = 0) Prophylaxis with unknown (n = 39)	Total cases of PJP (n = 1) Cases with CCRT (n = 1) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	Patient died. Lymphopenia grade ¾ (n = 26, 63%) Lymphopenia grade 4 cases (10.3%) Baseline steroid usage (n = 30)
Grossman, 2011[27]	GBM (n = 81) AA (n = 12) AO (n = 2)	NR	96 received RT + TMZ.	No prophylaxis (NR) Prophylaxis (NR) Prophylaxis "recommended"	Total cases of PJP (n = 1) Cases with CCRT (NR) Cases without CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Pneumonia not specified (n = 6)	PJP outcome (NR) CD4 count lowest at 255 2 months after starting RT + TMZ. 38 (40%) cases had CD4 counts below 200. Baseline steroid usage (n = 79)
Kim, 2011[28]	AA (n = 21) AO (n = 12)	2002	33 started RT + TMZ, and 22 subsequently started adjuvant TMZ.	No prophylaxis (NR) Prophylaxis (NR) Prophylaxis "recommended"	Total cases of PJP (n = 0) Cases with CCRT (n = 9) Cases without CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (n = 0) Cases with steroid (n = 15) Pneumonia not specified (n = 0)	Lymphopenia grade 3/4 (n = 0) Steroids during CCRT (n = 9) Steroids during adjuvant chemotherapy (n = 6)
Cao, 2011[29]	GBM (n = 112)	NR	112 treated with hypofractionated RT, 57 of whom received concurrent and adjuvant TMZ and 55 received RT alone initially.	No prophylaxis (n = 55) TMP-SMX (n = 57)	Total cases of PJP (n = 0) Pneumonia not specified (n = 1)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR) Median steroid dose 4 mg during RT + TMZ.
Demirici, 2011[30]	GBM (n = 142) AA (n = 30)	2007	172 initially treated with RT + TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 0) Cases with CCRT (n = 0) Cases with prophylaxis (n = 0) Cases without prophylaxis (n = 0) Cases with lymphopenia (n = 0) Cases with steroid (n = 0) Pneumonia not specified (n = 1)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)
Iliadis, 2012[31]	GBM (n = 65)	NR	65 initially treated with RT + TMZ, of whom 56 proceeded to adjuvant TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 1) Cases with CCRT (n = 1) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 2)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)
Malkoun, 2012[32]	GBM (n = 45)	2007	45 initially treated with RT + TMZ, and 37 subsequently received adjuvant TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 1) Cases with CCRT (n = 1) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (n = 8) Baseline steroid usage (NR)

(Table 3 continues on next page)

Study	Population	WHO	Intervention	PJP prophylaxis	PJP outcomes	Secondary outcomes
(Continued from previous page)						
Pitz, 2012[33]	GBM (n = 116)	NR	116 were initially treated with RT + TMZ, and 80 subsequently received adjuvant TMZ and *cis*-retinoic acid.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 0) Cases with CCRT (n = 0) Cases with prophylaxis (n = 0) Cases without prophylaxis (n = 0) Cases with lymphopenia (n = 0) Cases with steroid (n = 0) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)
Salmaggi, 2013[34]	GBM (n = 35)	NR	35 treated with surgically inserted carmustine wafers, daily TMZ for up to 6 months, and RT.	No prophylaxis (n = 0) Prophylaxis with unknown (n = 35)	Total cases of PJP (n = 0) Cases with CCRT (n = 0) Cases with prophylaxis (n = 0) Cases without prophylaxis (n = 0) Cases with lymphopenia (n = 0) Cases with steroid (n = 0) Pneumonia not specified (n = 2)	Lymphopenia grade 3/4 (n = 22) Baseline steroid usage (NR)
Tanaka, 2013[35]	GBM (n = 105)	NR	105 reviewed. 33 treated with the RT + TMZ and adjuvant TMZ. 72 received either sequential treatment, RT only, or unknown.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 1) Cases with CCRT (n = 0) Cases with RT only (n = 1) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 1)	Patient outcome NR Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)
Clarke, 2014[36]	GBM (n = 74)	NR	74 received RT + TMZ, followed by TMZ, bevacizumab, and erlotinib.	No prophylaxis (NR) Prophylaxis (NR) Prophylaxis was "encouraged" for patients on corticosteroids and during radiation with TMZ	Total cases of PJP (n = 1? pneumonitis secondary to either PJP or erlotinib) Cases with CCRT (n = 1?) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (n = 48) Cases with steroid (NR) Pneumonia not specified (NR)	Patient outcome NR Lymphopenia grade 3/4 (n = 48) Baseline steroid usage (NR)
Neuwelt, 2014[37]	GBM (n = 95) AA (n = 58) AO (n = 89)	NR	240 analyzed including 127 received RT + TMZ.	No prophylaxis (n = 240) Prophylaxis (n = 0)	Total cases of PJP (n = 1) Cases with CCRT (n = 1) Cases with prophylaxis (n = 0) Cases without prophylaxis (n = 1) Cases with lymphopenia (n = 1) Cases with steroid (NR) Pneumonia not specified (n = 0)	Patient hospitalized and fully recovered. Median nadir lymphocyte count 0.7 × 10^9/L. Extended steroid usage for 89% of patients.
Parisi, 2015[38]	GBM (n = 93) AA (n = 35)	NR	128 reviewed. 64 received RT and TMZ including 33 treated with RT + TMZ followed by adjuvant TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 0) Cases with CCRT (n = 0) Cases with prophylaxis (n = 0) Cases without prophylaxis (n = 0) Cases with lymphopenia (n = 0) Cases with steroid (n = 0) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)

(Table 3 continues on next page)

Study	Population	WHO	Intervention	PJP prophylaxis	PJP outcomes	Secondary outcomes
(Continued from previous page)						
Saran, 2021[39]	GBM (n = 36)	NR	36 enrolled in trial, including 20 who received RT + TMZ and afatinib, and 16 who received concurrent RT plus afatinib.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 2)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)
Lim, 2022[40]	GBM (n = 709)	NR	709 received RT + TMZ, including 355 additionally receiving nivolumab and 354 receiving placebo.	No prophylaxis (NR) Prophylaxis with unknown (n = 709)	Total cases of PJP (n = 1) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	Patient died. Lymphopenia grade 3/4 (n = 38) Baseline steroid usage (n = 209)
Peters, 2022[41]	GBM (n = 94) Grade 3 (n = 16)	NR	115 received RT + TMZ and were randomized to also receive naltrexone or placebo.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (n = 6) Cases with steroid (NR) Pneumonia not specified (n = 1)	Lymphopenia grade 3/4 (n = 6) Baseline steroid usage (NR)
Climans, 2022[42]	GBM, astrocytoma, oligodendroglioma (n = 5130)	NR	5130 included in cohort treated with RT + TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 38) Cases with CCRT (n = 38) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	PJP patient outcomes (NR) Trough lymphocyte count 0.4×10^9/L and 0.7×10^9/L for PJP and no-PJP groups respectively. Baseline dexamethasone dose 0.3 mg and 0.3 mg for PJP and no-PJP groups respectively.
Climans, 2022[43]	GBM (n = 2440) DA (n = 159) AA (n = 273) DO (n = 72) AO (n = 138) Unspecified (n = 143)	NR	3225 included in cohort treated with RT + TMZ.	No prophylaxis (n = 2577) TMP-SMX or dapsone (n = 648)	Total cases of PJP (n = 18) Cases with CCRT (n = 18) Cases with prophylaxis (n = 12) Cases without prophylaxis (n = 6) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 207)	PJP patient outcomes (NR) Lymphopenia grade 3/4 (NR) 39 cases (6.0%) and 108 cases (4.2%) of grade 3/4 leukopenia in prophylaxis and no-prophylaxis groups respectively. Baseline steroid usage in 441 cases (68.0%) and 1239 cases (48.0%) of prophylaxis and no-prophylaxis groups respectively.
Bruno, 2022[44]	GBM (n = 135)	NR	135 identified who underwent a surgical procedure, of whom 37 received hypofractionated TMZ + RT and 33 received conventional TMZ + RT.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (n = 0) Baseline steroid usage (NR)

(Table 3 continues on next page)

Study	Population	WHO	Intervention	PJP prophylaxis	PJP outcomes	Secondary outcomes
(Continued from previous page)						
Demircan, 2023[45]	GBM (n = 169)	2021	169 treated with RT + TMZ, of whom 133 proceeded to adjuvant TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 2) Cases with CCRT (n = 2) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 4)	PJP patient outcome (NR) 21 cases (12%) and 12 cases (7%) of "acute severe lymphopenia" (definition not reported) at end of RT and 1 month after RT respectively. Dexamethasone used in 76 cases (45%) during CCRT.
Omuro, 2022[46]	GBM (n = 542) GS (n = 18)	NR	275 treated with RT + TMZ, 278 treated with RT + nivolumab.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (n = 0) Cases with CCRT (n = 0) Cases with prophylaxis (n = 0) Cases without prophylaxis (n = 0) Cases with lymphopenia (n = 0) Cases with steroid (n = 0) Pneumonia not specified (n = 0)	Lymphopenia grade 3/4 (n = 12) Baseline steroid usage (n = 95, 33.9%)
Lassman, 2022[47]	GBM (n = 630) GS (n = 4) Other (n = 2) Missing (n = 3)	2016	316 treated with RT + TMZ + placebo, 323 treated with RT + TMZ + depatux-M.	No prophylaxis (n = 0) Prophylaxis with unknown (n = 639)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (n = 41) Baseline steroid usage (n = NR)
Sim, 2022[48]	GBM (n = 103)	2016	103 treated with RT + TMZ, 69 of whom allocated to MTZ TMZ + nivolumab and 34 allocated to MTZ TMZ alone.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 1)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (n = 56, 54.4%)
Arnold, 2024[49]	GBM (n = 144) Astrocytoma grade 4 (n = 21) DA (n = 9) AA (n = 16) DO (n = 7) AO (n = 7)	2021	217 treated with RT + TMZ.	No prophylaxis (n = 3) TMP-SMX (n = 144) Pentamidine (n = 69) Dapsone (n = 1)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)
Sloan, 2024[50]	GBM (n = 31)	NR	31 treated with RT + TMZ.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 1)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)

(Table 3 continues on next page)

Study	Population	WHO	Intervention	PJP prophylaxis	PJP outcomes	Secondary outcomes
(Continued from previous page)						
Goldlust, 2024[51]	GBM (n = 13)	NR	13 treated with TMZ + RT + TTF followed by maintenance TMZ + TTF.	No prophylaxis (NR) Prophylaxis (NR)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (n = 1)	Lymphopenia grade 3/4 (n = 2) Baseline steroid usage (NR)
Narang, 2025[52]	Astrocytoma grade 4 (n = 267)	NR	267 treated with RT + TMZ.	No prophylaxis (n = 0) Cotrimoxazole (n = 267)	Total cases of PJP (NR) Cases with CCRT (NR) Cases with prophylaxis (NR) Cases without prophylaxis (NR) Cases with lymphopenia (NR) Cases with steroid (NR) Pneumonia not specified (NR)	Lymphopenia grade 3/4 (NR) Baseline steroid usage (NR)

List of studies included in the systematic review detailed by histopathologic sample sizes, World Health Organization glioma classification version, types of interventions, usage of antibiotic prophylaxis, numbers of PJP cases, outcomes of infections, and associated cytopenia and steroid usage. NR: not reported; TMZ: temozolomide; RT: radiation therapy; CCRT: concurrent chemoradiation; HGG: high-grade glioblastoma; GBM: multiforme; DA: diffuse astrocytoma; AA: anaplastic astrocytoma; DO: diffuse oligodendroglioma; AO: anaplastic astrocytoma; GS: gliosarcoma; OS: overall survival; PFS: progression free survival; QOL: quality of life; MTD: maximum tolerated dose; KPS: Karnofsky performance scale; ORR: objective response rate; RFS: recurrence-free interval; PJP: *pneumocystis jirovecii* pneumonia.

Table 3: **Key populations, interventions, and outcomes of included studies.**

unconfirmed case of PJP pneumonitis occurred during maintenance TMZ in a trial where prophylaxis was recommended but not documented.

Seven studies provided detailed, patient-level reporting of both PJP incidence and prophylaxis.[6,19,26,34,37,40,43] These included 4883 patients: 4484 treated with TMZ-RT, 113 with TMZ alone, and 286 with RT alone. Across these studies, there were 24 PJP cases (0–18 per study): 23 cases among TMZ-RT group and one in the RT-only group. The overall incidence of PJP amongst TMZ-RT recipients was 0.5% (23/4484). Among those, 1765 of 4484 (39.4%) received prophylaxis and 2719 (60.6%) did not. The PJP incidence was 0.8% (14/1765) with prophylaxis and 0.3% (9/2719) without.

Proportional meta-analysis

Across 24 studies explicitly reporting confirmed PJP cases, encompassing 12,056 patients with 71 documented PJP events, the pooled incidence of PJP was 0.74% (95% CI, 0.59–0.93%; 95% prediction interval, 0.58–0.96%) based on the random-effects model with logit transformation (Fig. 2). Statistical heterogeneity was negligible ($Q = 23.3$, $df = 23$, $p = 0.44$; $I^2 = 1.4\%$; $\tau^2 = 0.0045$) indicating highly consistent low risk across studies (Fig. 2).

Sensitivity analyses confirmed the robustness of this estimate. Using PFT transformation, the pooled incidence was 0.1% (95% CI, 0.07–0.2%; 95% prediction interval, 0.0–0.4%), which likewise supports an incidence well below 1%. In this model, heterogeneity was moderate ($Q = 39.7$, $df = 23$, $p = 0.017$; $I^2 = 42.0\%$; $\tau^2 = 0.0006$), reflecting some variability across study estimates but with minimal between-study variance. Results were similar when alternative effect-size transformations (raw proportions) or different model specifications (fixed-versus random-effects, Hartung-Knapp adjustment) were applied. There was no single study that meaningfully altered the pooled estimate in leave-one-out analyses. Assessment of small-study effects showed no evidence of funnel plot asymmetry (Fig. 3). Egger's regression test was non-significant (logit: $p = 0.75$; PFT: $p = 0.54$), and the trim-and-fill method did not impute additional studies under the logit model. Under the PFT model, three studies were imputed, but the adjusted pooled incidence remained well below 1%.

Timing of PJP and prophylaxis

Six studies[6,19,26,34,37,43] provided sufficient detail to examine the temporal relationship between TMZ-RT and PJP and stratify by prophylaxis. These included 3775 TMZ-RT patients with 22 PJP cases: two during chemoradiation, 18 within 90 days of starting chemoradiation, one during maintenance TMZ, and one after chemoradiation without maintenance chemotherapy. Twenty of 22 cases (90.9%) occurred during or shortly after chemoradiation. Limiting to these 20 cases, the PJP incidence was 1.1% (12/1056) with and 0.3% (8/2719) without prophylaxis.

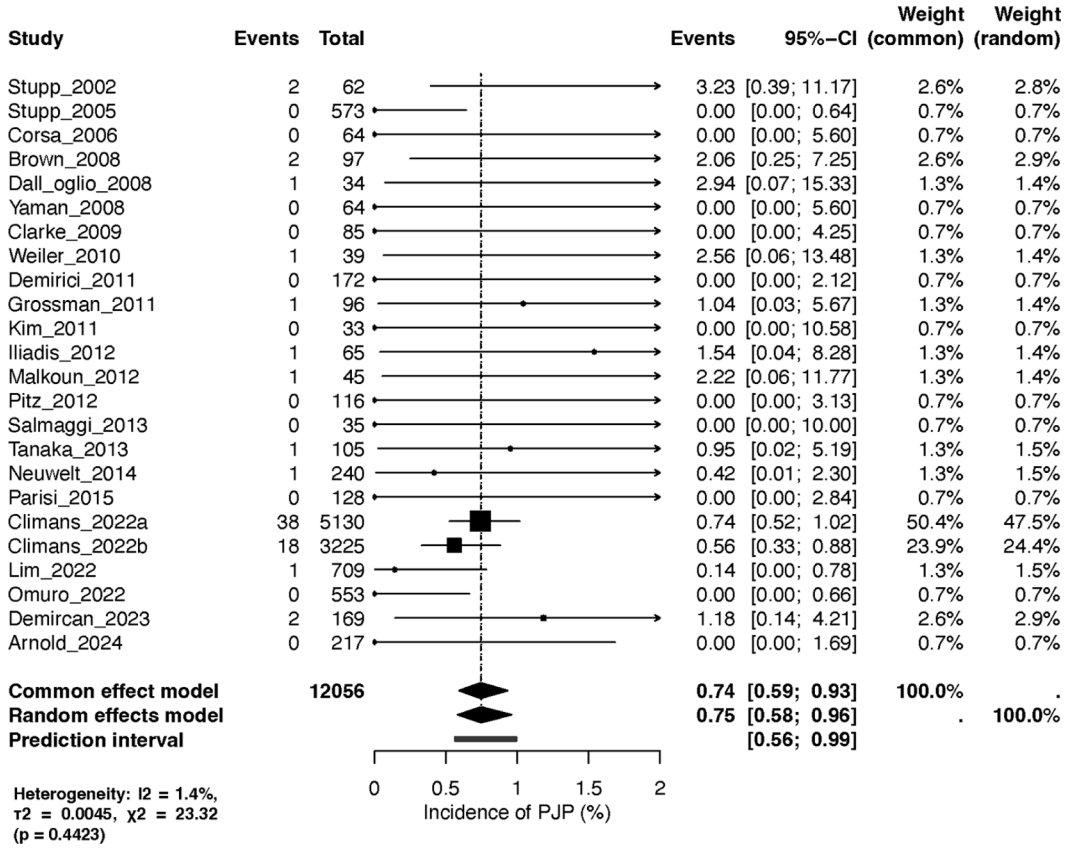

Fig. 2: Forest plot outlining study-specific and pooled estimates of *pneumocystis jirovecii* pneumonia (PJP) incidence and corresponding 95% confidence intervals (CIs) using a random-effects model with logit transformation. Heterogeneity was expressed using the I^2 statistic, τ^2 (between-study variance), and χ^2 (Cochran's Q) test.

Steroid exposure

Baseline corticosteroid use (at therapy initiation) was reported in 13 studies.[19,21,22,24,26–28,37,40,43,45,46,48] After excluding one study that did not detail the number of patients exposed,[21] there was a total of 5908 patients evaluable and treated: 5229 with TMZ-RT, 280 with TMZ-RT and an investigational agent, 113 TMZ without RT, and 286 with RT alone. Overall, 2898 patients (49.1%) were on baseline steroids (range: 27.3 to 82.3%; median 49.5%, interquartile range 32.0–66.0%). These studies documented 27 PJP cases (0–18 per study; one study unreported). An exploratory study-level analysis demonstrated a moderate positive correlation between corticosteroid exposure and reported PJP incidence (Spearman's $\rho = 0.67$, $p = 0.02$). Due to the low number of infectious events and incomplete reporting of steroid exposure at the time of PJP diagnosis, a quantitative assessment of corticosteroids as an independent risk factor was not feasible.

Lymphopenia

Grade 3–4 lymphopenia was reported in 16 studies.[6,22,23,25,26,28,32,34,36,37,40,41,45–47,51] Excluding one study reporting only median nadir values,[37] data came from 2705 patients (2102 TMZ-RT and 603 TMZ-RT with investigational agent). Overall, 319 of 2102 TMZ-RT patients (15.2%) developed grade 3–4 lymphopenia (range: 0–49%; median 21.2%, IQR 6.0–38%). Ten PJP cases occurred among studies reporting lymphopenia status and PJP occurrence, and only three studies reported lymphopenia status specifically at time of PJP diagnosis.[6,22,37] 286 TMZ-RT patients with five PJP cases, of whom two (40.0%) had concurrent lymphopenia. The observed PJP rate in this subset was 1.7% (5/286): 0.7% (2/286) with and 1.0% (3/286) without lymphopenia. Due to the low event rate of PJP and incomplete reporting, no meaningful association between lymphopenia and PJP risk could be established.

Discussion

Concurrent chemoradiation with temozolomide is central to glioma therapy. However, radiation can cause immune dysfunction by directly damaging and reducing trafficking of circulating lymphocytes.[58] TMZ independently and cumulatively depletes CD4 T cells.[59]

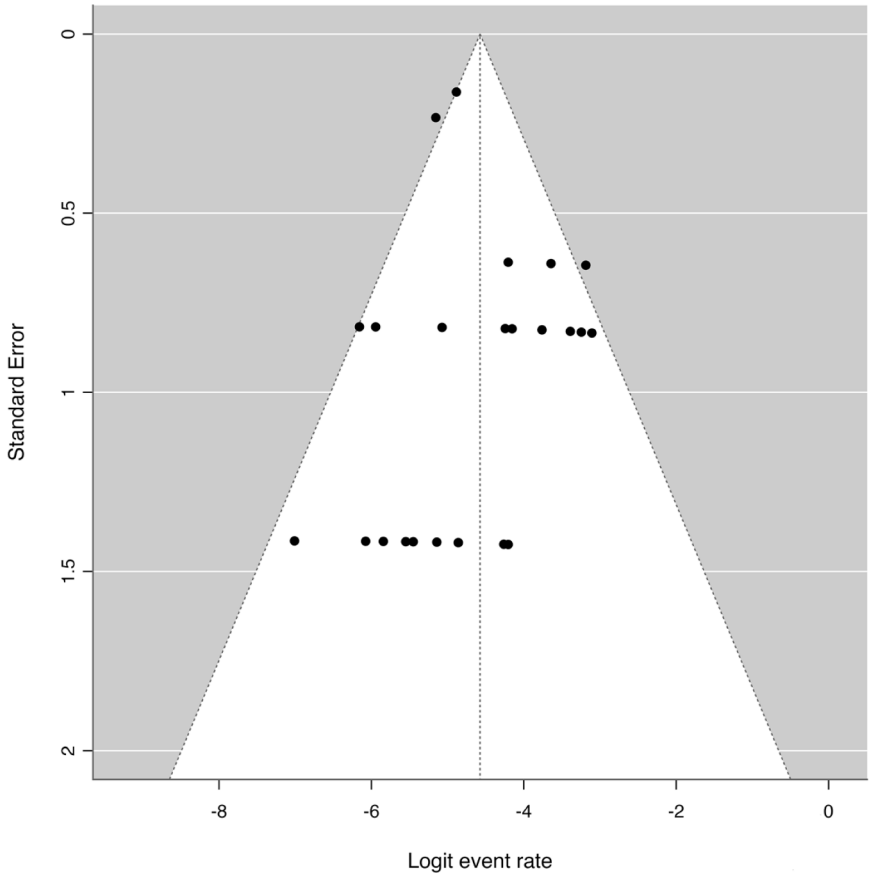

Fig. 3: Funnel plot assessing publication bias in proportional meta-analysis of *pneumocystis jirovecii* pneumonia (PJP) incidence through the relationship between the logit-transformed event rate and standard error for individual studies. The vertical line denotes the pooled estimate from the random-effects model, and the dashed lines represent the 95% pseudo-confidence limits.

These biologic effects impair T cell activity and recovery and underlie a patient's susceptibility to opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PJP). Accordingly, regulatory drug monographs (FDA, Health Canada, and CCO) mandate PJP prophylaxis during TMZ-RT.

Despite these concerns, the true incidence of PJP associated with TMZ-RT has been uncertain. This systematic review provides the most comprehensive synthesis to date, incorporating studies through to May 1, 2025, to quantify the incidence of PJP in glioma patients receiving TMZ-RT and to critically evaluate the evidence underpinning current prophylaxis guidelines.

Our systematic review consolidated 35 studies (13,637 patients; 12,301 received TMZ-RT). We found 71 PJP cases among 12,056 evaluable patients. Most infections occurred during or within 90 days of starting radiotherapy. Pooled random-effects meta-analysis yielded a stable incidence of 0.74% (95% CI, 0.59–0.93%), with low heterogeneity and no signal of publication bias. Prophylaxis patterns were heterogeneous: 44.9% of TMZ-RT patients overall received no prophylaxis, yet PJP rates remained very low (0.8% with prophylaxis and 0.3% without prophylaxis among studies reporting these data). Corticosteroid exposure at baseline was frequent (49.1% overall), and 15.2% of TMZ-RT patients developed grade 3–4 lymphopenia, but sparse and inconsistent reporting precluded robust risk modeling.

Limitations of this review included the rarity of PJP, and absence of randomized trials directly addressing prophylaxis making reliance on observational data a necessity. Furthermore, reporting of prophylaxis details (drug, dose, timing, duration), PJP diagnostic confirmation, and immune risk factors (steroid dose and duration, lymphopenia at infection) was inconsistent, limiting secondary analyses. Future studies should systematically collect and report corticosteroid exposure, particularly timing, dosage, and duration, to better quantify its contribution to PJP risk in this population. Many retrospective cohorts were at risk of bias; however, the pooled estimate was driven by large, provincial

datasets and prospective studies, which showed minimal heterogeneity, and was stable across sensitivity analyses. The review was restricted to English-language studies, a factor that could limit generalizability and introduce language bias.

Overall, the absolute risk of PJP during or shortly after TMZ-RT appears well below the 3.5% threshold typically used to justify routine prophylaxis. TMP-SMX, the most common prophylactic agent, carries meaningful toxicity, including myelosuppression, renal impairment, hyperkalemia, nausea, and drug interactions, and potentially life-threatening reactions such as Stevens-Johnson Syndrome, anaphylaxis, and agranulocytosis. Prior population-based analyses found no survival or hospitalization benefit from prophylaxis; the number needed to harm (NNH) for prophylaxis-induced neutropenia was 39 compared with a number needed to treat (NNT) of 288 to prevent one PJP hospitalization.[43] In our study, the apparent higher PJP rate in the prophylaxis subgroup most likely reflects confounding by indication (i.e, prophylaxis was preferentially given to higher-risk patients); under these conditions, NNT/NNH estimates would be misleading. Importantly, the pooled PJP incidence was stable across all sensitivity analyses and consistently less than 3.5% across subgroups. Thus, any small absolute risk reduction from routine prophylaxis must be balanced against it potential for clinically meaningful harm.

Given the low event rate, a randomized prophylaxis trial is neither feasible nor cost-effective. Current evidence supports an individualized, risk-adapted approach: consider prophylaxis for patients with high-dose or prolonged corticosteroids, those with profound lymphopenia, frailty, or major comorbidities, but not as a universal requirement. Additional studies refining risk stratification and clarifying incidence across diverse populations and practice settings could further inform prophylaxis decisions.

Contributors

JJ: Literature search, Data abstraction, Data synthesis, Manuscript writing, Figure generation, Critical editing. BA: Literature search, Data abstraction, Statistical methods, Manuscript writing, Figure generation, Critical editing. AABB: Conceptualization, Methodology, Literature search, Data abstraction, Data synthesis, Critical editing. MM: Data abstraction, Manuscript review and editing. FR: Data abstraction, Manuscript review and editing. JL: Data abstraction, Critical editing. DC: Data abstraction, Manuscript review and editing. FF: Data abstraction, Manuscript review and editing. VL: Data abstraction, Manuscript review and editing. SFL: Manuscript writing, Figure generation, Critical editing. TLN.: Conceptualization, Methodology, Literature search, Data abstraction, Data synthesis, Manuscript writing, Critical editing, Supervision. JJ, BA, and TLN have verified the underlying data. All authors read and approved the final version of the manuscript.

Data sharing statement

The data are reported in previously published studies an accessible in corresponding publications. The datasets of abstracted and analyzed materials are available from the corresponding author on reasonable request. The original protocol for this systematic review was registered in PROSPERO under the ID: CRD42021292396.

Declaration of interests

BA has received payment or honoraria from Merck Sharp & Dohme, AstraZeneca, and Novartis, and support for meetings or travel from Merck Sharp & Dohme. AABB has received payment or honoraria from Janssen Pharmaceuticals. DC has received payment or honoraria from Bristol-Myers Squibb, Pfizer, and EMD Serrono, and support for meetings or travel from EMD Serrono. TL has received grants from the Canadian Institute of Health Research, The Ottawa Hospital Academic Medical Organization, Gavin Murphy Fund, and Canadian Cancer Society Research Institute, payment or honoraria from Novartis Canada, Gilead Sciences, and AstraZeneca, and has participated on data safety monitoring or advisory boards for Knight Therapeutics, Novartis Canada, and Gilead Sciences. All other authors declare no conflicts of interest.

Acknowledgements

The authors would like to thank Ms. Risa Shorr (Research Librarian) for developing the search strategy for this systematic review.

The authors would also like to thank the Deanship of Graduate Studies and Scientific Research at Qassim University for financial support for the Article Processing Charge (QU-APC-2025).

No AI tools were used in the assessment and preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2025.103715.

References

1 Medrano FJ, Montes-Cano M, Conde M, et al. Pneumocystis jirovecii in general population. *Emerg Infect Dis*. 2005;11(2):245–250. https://doi.org/10.3201/eid1102.040487.
2 Green H, Paul M, Vidal L, Leibovici L. Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients. *Cochrane Database Sys Rev*. 2007;18(3):CD005590. https://doi.org/10.1002/14651858.CD005590.pub2.
3 Roux A, Canet E, Valade S, et al. Pneumocystis jirovecii pneumonia in patients with or without AIDS, France. *Emerg Infect Dis*. 2014;20(9):1490–1497. https://doi.org/10.3201/eid2009.131668.
4 Sepkowitz KA, Brown AE, Armstrong D. Pneumocystis carinii pneumonia without acquired immunodeficiency syndrome. More patients, same risk. *Arch Intern Med*. 1995;155(11):1125–1128. https://doi.org/10.1001/archinte.1995.00430110015002.
5 Hughes WT, Feldman S, Aur RJ, Verzosa MS, Hustu HO, Simone JV. Intensity of immunosuppressive therapy and the incidence of Pneumocystis carinii pneumonitis. *Cancer*. 1975;36(6):2004–2009.
6 Stupp R, Dietrich P-Y, Ostermann Kraljevic S, et al. Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. *J Clin Oncol*. 2002;20(5):1375–1382. https://doi.org/10.1200/JCO.2002.20.5.1375.
7 Merck, Temodar (temozolomide) [package insert]. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021029s031lbl.pdf. Accessed February 20, 2024.
8 Health Canada. *ACT Temozolomide capsules. Product monograph*. Ottawa, ON: Health Canada; 2023. https://pdf.hres.ca/dpd_pm/00030640.PDF. Accessed November 30, 2024.
9 Cancer Care Ontario. Temozolomide capsules. Product monograph. Toronto, ON: CCO Formulary; 2-21. https://www.cancercareontario.ca/en/drugformulary/drugs/monograph/43726. Accessed November 30, 2024.
10 National Comprehensive Caner Network. Prevention and treatment of cancer-related infections. Version 3.2024. Plymouth meeting, PA: NCCN. https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf; 2024. Accessed November 30, 2024.

11 Taplitz RA, Kennedy EB, Bow EJ, et al. Antimicrobial prophylaxis for adult patients with cancer-related immunosuppression: ASCO and IDSA Clinical Practice Guideline update. *J Clin Oncol*. 2018;36(30):3043–3054. https://doi.org/10.1200/JCO.18.00374.
12 Roth P, Pace A, Le Rhun E, et al. Neurological and vascular complications of primary and secondary brain tumours: EANO-ESMO Clinical Practice Guidelines for prophylaxis, diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(2):171–182. https://doi.org/10.1016/j.annonc.2020.11.003.
13 Masters PA, O'Bryan TA, Zurlo J, Miller DQ, Joshi N. Trimethoprim-sulfamethoxazole revisited. *Arch Intern Med*. 2003;163(4):402–410. https://doi.org/10.1001/archinte.163.4.402.
14 Skorupan N, Ranjan S, Mehta S, et al. Pneumocystis jirovecii prophylaxis in patients treated for high-grade gliomas: a survey among neuro-oncologists. *Neurooncol Pract*. 2019;6(4):321–326. https://doi.org/10.1093/nop/npy049.
15 Beltran-Bless A-A, Alshamsan B, Jia J, et al. Perception of pneumocystis jirovecii pneumonia (PJP) prophylaxis in glioma patients receiving concurrent temozolomide and radiation- a patient and physician survey. *J Neurooncol*. 2024;169(3):625–632. https://doi.org/10.1007/s11060-024-04764-6.
16 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. https://doi.org/10.1136/bmj.n71.
17 Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. https://doi.org/10.1136/bmj.d5928.
18 Haffar S, Bazerbachi F, Prokop L, Watt KD, Murad MH, Chari ST. Frequency and prognosis of acute pancreatitis associated with fulminant or non-fulminant acute hepatitis A: a systematic review. *Pancreatology*. 2017;17(2):166–175. https://doi.org/10.1016/j.pan.2017.02.008.
19 Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987–996. https://doi.org/10.1056/NEJMoa043330.
20 Corsa P, Parisi S, Raguso A, et al. Temozolomide and radiotherapy as first-line treatment of high-grade gliomas. *Tumori*. 2006;92(4):299–305. https://doi.org/10.1177/030089160609200407.
21 Gerber DE, Grossman SA, Zeltzman M, Parisi MA, Kleinberg L. The impact of thrombocytopenia from temozolomide and radiation in newly diagnosed adults with high-grade gliomas. *Neuro Oncol*. 2007;9(1):47–52. https://doi.org/10.1215/15228517-2006-024.
22 Brown PD, Krishnan S, Sarkaria JN, et al. Phase I/II trial of erlotinib and temozolomide with radiation therapy in the treatment of newly diagnosed glioblastoma multiforme: North Central Cancer Treatment Group Study N0177. *J Clin Oncol*. 2008;26(34):5603–5609. https://doi.org/10.1200/JCO.2008.18.0612.
23 Dall'oglio S, D'Amico A, Pioli F, et al. Dose-intensity temozolomide after concurrent chemoradiotherapy in operated high-grade gliomas. *J Neurooncol*. 2008;90(3):315–319. https://doi.org/10.1007/s11060-008-9663-9.
24 Yaman E, Buyukberber S, Uner A, et al. Temozolomide in newly diagnosed malignant gliomas: administered concomitantly with radiotherapy, and thereafter as consolidation treatment. *Onkologie*. 2008;31(6):309–313. https://doi.org/10.1159/000127252.
25 Clarke JL, Iwamoto FM, Sul J, et al. Randomized phase II trial of chemoradiotherapy followed by either dose-dense or metronomic temozolomide for newly diagnosed glioblastoma. *J Clin Oncol*. 2009;27(23):3861–3867. https://doi.org/10.1200/JCO.2008.20.7944.
26 Weiler M, Hartmann C, Wiewrodt D, et al. Chemoradiotherapy of newly diagnosed glioblastoma with intensified temozolomide. *Int J Radiat Oncol Biol Phys*. 2010;77(3):670–676. https://doi.org/10.1016/j.ijrobp.2009.05.031.
27 Grossman SA, Ye X, Lesser G, et al. Immunosuppression in patients with high-grade gliomas treated with radiation and temozolomide. *Clin Cancer Res*. 2011;17(16):5473–5480. https://doi.org/10.1158/1078-0432.CCR-11-0774.
28 Kim WH, Yoon SH, Kim CY, et al. Temozolomide for malignant primary spinal cord glioma: an experience of six cases and a literature review. *J Neurooncol*. 2011;101(2):247–254. https://doi.org/10.1007/s11060-010-0249-y.
29 Cao JQ, Fisher BJ, Bauman GS, Megyesi JF, Watling CJ, Macdonald DR. Hypofractionated radiotherapy with or without concurrent temozolomide in elderly patients with glioblastoma multiforme: a review of ten-year single institutional experience. *J Neurooncol*. 2012;107(2):395–405. https://doi.org/10.1007/s11060-011-0766-3.
30 Demirci U, Buyukberber S, Coskun U, et al. Long term experience in high grade glial tumors with temozolomide. *J BUON*. 2012;17(2):357–362.
31 Iliadis G, Kotoula V, Chatzisotiriou A, et al. Volumetric and MGMT parameters in glioblastoma patients: survival analysis. *BMC Cancer*. 2012;12:3. https://doi.org/10.1186/1471-2407-12-3.
32 Malkoun N, Chargari C, Forest F, et al. Prolonged temozolomide for treatment of glioblastoma: preliminary clinical results and prognostic value of p53 overexpression. *J Neurooncol*. 2012;106(1):127–133. https://doi.org/10.1007/s11060-011-0643-0.
33 Pitz MW, Lipson M, Hosseini B, et al. Extended adjuvant temozolomide with cis-retinoic acid for adult glioblastoma. *Curr Oncol*. 2012;19(6):308–314. https://doi.org/10.3747/co.19.1151.
34 Salmaggi A, Milanesi I, Silvani A, et al. Prospective study of carmustine wafers in combination with 6-month metronomic temozolomide and radiation therapy in newly diagnosed glioblastoma: preliminary results. *J Neurosurg*. 2013;118(4):821–829. https://doi.org/10.3171/2012.12.JNS111893.
35 Tanaka S, Meyer FB, Buckner JC, Uhm JH, Yan ES, Parney IF. Presentation, management, and outcome of newly diagnosed glioblastoma in elderly patients. *J Neurosurg*. 2013;118(4):786–798. https://doi.org/10.3171/2012.10.JNS112268.
36 Clarke JL, Molinaro AM, Phillips JJ, et al. A single-institution phase II trial of radiation, temozolomide, erlotinib, and bevacizumab for initial treatment of glioblastoma. *Neuro Oncol*. 2014;16(7):984–990. https://doi.org/10.1093/neuonc/nou029.
37 Neuwelt AJ, Nguyen TM, Fu R, et al. Incidence of *Pneumocystis jirovecii* pneumonia after temozolomide for CNS malignancies without prophylaxis. *CNS Oncol*. 2014;3(4):267–273. https://doi.org/10.2217/cns.14.24.
38 Parisi S, Corsa P, Raguso A, et al. Temozolomide and radiotherapy versus radiotherapy alone in high grade gliomas: a very long term comparative study and literature review. *BioMed Res Int*. 2015;2015:620643. https://doi.org/10.1155/2015/620643.
39 Saran F, Welsh L, James A, McBain C, et al. Afatinib and radiotherapy, with or without temozolomide, in patients with newly diagnosed glioblastoma: results of a phase I trial. *J Neurooncol*. 2021;155(3):307–317. https://doi.org/10.1007/s11060-021-03877-6.
40 Lim M, Weller M, Idbaih A, et al. Phase III trial of chemoradiotherapy with temozolomide plus nivolumab or placebo for newly diagnosed glioblastoma with methylated MGMT promoter. *Neuro Oncol*. 2022;24(11):1935–1949. https://doi.org/10.1093/neuonc/noac116.
41 Peters KB, Affronti ML, Woodring S, et al. Effects of low-dose naltrexone on quality of life in high-grade glioma patients: a placebo-controlled, double-blind randomized trial. *Support Care Cancer*. 2022;30(4):3463–3471. https://doi.org/10.1007/s00520-021-06738-0.
42 Climans SA, Mason WP, Grunfeld E, Chan K. Clinical features of glioma patients who develop pneumocystis pneumonia with temozolomide chemoradiotherapy. *J Neurooncol*. 2022;159(3):665–674. https://doi.org/10.1007/s11060-022-04109-1.
43 Climans SA, Grunfeld E, Mason WP, Chan KKW. Effectiveness and safety of pneumocystis pneumonia prophylaxis for patients receiving temozolomide chemoradiotherapy. *Neuro Oncol*. 2022;24(10):1738–1748. https://doi.org/10.1093/neuonc/noac072.
44 Bruno F, Pellerino A, Pronello E, et al. Elderly gliobastoma patients: the impact of surgery and adjuvant treatments on survival: a single institution experience. *Brain Sci*. 2022;12(5):632. https://doi.org/10.3390/brainsci12050632.
45 Demircan NV, Erpolat OP, Guzel C, Senturk E, Bora H, Karahacioglu E. The assessment of clinical outcomes and prognostic factors in glioblastoma patients. *Turk Neurosurg*. 2023;33(5):870–886. https://doi.org/10.5137/1019-5149.JTN.40460-22.3.
46 Omuro A, Brandes AA, Carpentier AF, et al. Radiotherapy combined with nivolumab or temozolomide for newly diagnosed glioblastoma with unmethylated MGMT promoter: an international randomized phase III trial. *Neuro Oncol*. 2023;25(1):123–134. https://doi.org/10.1093/neuonc/noac099.
47 Lassman AB, Pugh SL, Wang TJC, et al. Depatuxizumab mafodotin in EGFR-amplified newly diagnosed glioblastoma: a phase III randomized clinical trial. *Neuro Oncol*. 2023;25(2):339–350. https://doi.org/10.1093/neuonc/noac173.

48 Sim H-W, Wachsmuth L, Barnes EH, et al. NUTMEG: a randomized phase II study of nivolumab and temozolomide versus temozolomide alone in newly diagnosed older patients with glioblastoma. *Neurooncol Adv*. 2023;5(1):vdad124. https://doi.org/10.1093/noajnl/vdad124.

49 Arnold LM, Hoshina Y, Lee H, Colman H, Mendez J. Effect of Pneumocystis jirovecii pneumonia prophylaxis on hematologic toxicity in patients receiving chemoradiation for primary brain tumors. *J Neurooncol*. 2024;167(1):211–217. https://doi.org/10.1007/s11060-024-04588-4.

50 Sloan AE, Winter K, Gilbert MR, et al. NRG-BN002: phase I study of ipilimumab, nivolumab, and the combination in patients with newly diagnosed glioblastoma. *Neuro Oncol*. 2024;26(9):1628–1637. https://doi.org/10.1093/neuonc/noae058.

51 Goldlust SA, Singer S, Cappello LA, et al. Phase 1 study of concomitant tumor treating fields and temozolomide chemoradiation for newly diagnosed glioblastoma. *Neurooncol Adv*. 2024;6(1):vdae129. https://doi.org/10.1093/noajnl/vdae129.

52 Narang K, Kataria T, Bisht SS, et al. Contemporary long-term survival outcomes and prognostic factors in adult grade 4 Astrocytoma: an institutional analysis. *Clin Oncol*. 2025;40:103788. https://doi.org/10.1016/j.clon.2025.103788.

53 Kleihues P, Burger PC, Scheithauer BW. The new WHO classification of brain tumours. *Brain Pathol*. 1993;3(3):255–268. https://doi.org/10.1111/j.1750-3639.1993.tb00752.x.

54 Kleihues P, Cavenee WK, eds. *World Health Organisation classification of tumours: pathology and genetics of tumours of the nervous system*. Lyon: IARC Press; 2000.

55 Kleihues P, Louis DN, Scheithauer BW, et al. The WHO classification of tumors of the nervous system. *J Neuropathol Exp Neurol*. 2002;61(3):215–229. https://doi.org/10.1093/jnen/61.3.215.

56 Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO classification of tumours of the central nervous system. *Acta Neuropathol*. 2007;114(2):97–109. https://doi.org/10.1007/s00401-007-0243-4.

57 Louis DN, Perry A, Wesseling P, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. *Neuro Oncol*. 2021;23(8):1231–1251. https://doi.org/10.1093/neuonc/noab106.

58 Prades-Sagarra E, Yaromina A, Dubois LJ. Understanding the impact of radiation-induced lymphopenia: preclinical and clinical research perspectives. *Clin Transl Radiat Oncol*. 2024;49:100852. https://doi.org/10.1016/j.ctro.2024.100852.

59 Su YB, Sohn S, Krown SE, et al. Selective CD4+ lymphopenia in melanoma patients treated with temozolomide: a toxicity with therapeutic implications. *J Clin Oncol*. 2004;22(4):610–616. https://doi.org/10.1200/JCO.2004.07.060.