Congress of Neurological Surgeons Systematic Review and Evidence-Based Guidelines for the Treatment of Adults With WHO Grade II Diffuse Glioma: Update

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Recommendations are re-published with permission from Springer Nature. The full guideline can be seen online at Morrow K, Sloan A, Olson JJ, et al. Congress of Neurological Surgeons systematic review and evidence-based guidelines on the management of recurrent diffuse low-grade glioma: update. *J Neurooncol*. 2025;171:105-130. https://doi.org/10.1007/s11060-024-04838-5

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BACKGROUND: The management of World Health Organization (WHO) grade II diffuse glioma is an important facet of all physicians involved in neuro-oncology.
OBJECTIVE: This is an update of the evidence-based guidelines for management of WHO grade II diffuse gliomas published by the Congress of Neurological Surgeons and American Association of Neurological Surgeons in 2015.
METHODS: The medical literature from January 1, 2013, through January 31, 2020, was searched to determine if information was available to update, modify, or create new recommendations related to imaging, surgical approaches, neuropathology and molecular markers, radiotherapy, chemotherapy, and management of tumor recurrence.
RESULTS: The writing group used the information from the updated literature search to formulate recommendations based on this evidence and not simply built on biased consensus or expert opinion.
CONCLUSION: This series of guideline documents provides an update of the information and recommendations provided in the 2015 version. It sets a benchmark as to the published information we have to support the management of this difficult disease. It also provides clues to key investigations that are necessary to move us toward effective control of WHO grade II diffuse gliomas.

KEY WORDS: WHO grade II diffuse glioma, Low-grade glioma, Imaging, Surgery, Radiation therapy, Chemotherapy, Guidelines

ABBREVIATIONS: CNS, Congress of Neurological Surgeons; **IDH,** isocitrate dehydrogenase; **LGG,** low grade glioma; **OS,** overall survival; **RT,** radiation therapy; **WHO,** World Health Organization.

RECOMMENDATIONS

Imaging

Recommendations from the Prior Version of These Guidelines Without Change

Level II: In patients with a suspected brain tumor, the minimum MRI examination should be an anatomic examination with both T2-weighted and pregadolinium and postgadolinium contrast-enhanced T1-weighted imaging.

Level II: In patients with a suspected brain tumor, anatomic imaging sequences should include T1-weighted and T2-weighted and fluid attenuation inversion recovery magnetic resonance (MR) sequences and will include T1-weighted imaging after the administration of gadolinium-based contrast. Computed tomography can provide additional information regarding calcification or hemorrhage, which may narrow the differential diagnosis. At a minimum, these anatomic sequences can help identify a lesion as well as its location and potential for surgical intervention.

Level II: In patients with a diagnosis of low grade glioma (LGG), anatomic imaging sequences should include T2/fluid attenuation inversion recovery MR sequences and T1-weighted imaging before and after the administration of gadolinium-based contrast. Serial imaging should be performed to identify new areas of contrast enhancement or significant change in tumor size, which may signify transformation to a higher grade.

Level III: Advanced imaging utility may depend on tumor subtype. Multicenter clinical trials with larger cohorts are needed. For astrocytic tumors, baseline and longitudinal elevations in tumor perfusion as assessed by dynamic susceptibility contrast perfusion MRI are associated with shorter time to tumor progression but can be difficult to standardize in clinical practice. For oligodendrogliomas and mixed gliomas, magnetic resonance spectroscopy may be helpful for identification of progression.

Updated Recommendations from the Prior Version of These Guidelines

Level II: The use of diffusion imaging and dynamic susceptibility contrast, dynamic contrast enhancement, and arterial spin labeling sequences is suggested to differentiate World Health Organization (WHO) grade II diffuse glioma from higher grade gliomas when this is not accomplished by T2-weighted and pregadolinium and postgadolinium contrast-enhanced T1-weighted imaging.

Level III: The use of diffusion and perfusion is suggested for obtaining information in genomics, prognosis, and post-treatment monitoring when this information would be of value to the clinician and is not obtained through other methods.

Level III: The use of MR spectroscopy is suggested to differentiate WHO grade II diffuse glioma from higher-grade gliomas when this is not accomplished by standard MRI, perfusion, and diffusion techniques and when such information would be of value to the clinician.

New Recommendations

Level III: If not already evident by MRI studies, the addition of amino acid positron emission tomography (PET) with fluoroethyl-L-tyrosine and dihydroxy-6-fluoro-phenylalanine as a tracer is suggested to help determine if a brain lesion is a low-grade glioma or high-grade glioma.

Level III: If the standard clinical prognostic parameters are unclear and novel PET tracers are available, the clinician may consider fluoroethyl-L-tyrosine to assist in determination of prognosis in an individual with grade II diffuse glioma.

Level III: Clinicians may use dihydroxy-6-fluoro-phenylalanine PET in addition to MRI if additional information is required for detection of tumor progression.

Surgery

Unchanged Recommendations from the Prior Version of These Guidelines

Level II: It is recommended that gross total resection or subtotal resection be accomplished instead of biopsy alone when safe and feasible so as to decrease the frequency of tumor progression recognizing that the rate of progression after gross total resection is fairly high.

Level III: Greater extent of resection can improve overall survival (OS) in WHO grade II diffuse gliomas patients.

Level III: The use of intraoperative MRI is suggested to increase the extent of resection for adults with WHO grade II diffuse glioma.

Updated Recommendation from the Prior Version of These Guidelines

Level III: In adults with imaging suggestive of a WHO grade II diffuse gliomas (oligodendrogliomas or astrocytomas), surgical resection is suggested over observation or biopsy to improve overall survival.

Level III: In adults with imaging consistent with a WHO grade II diffuse glioma who present with seizure activity, surgical resection of greater than 90% of the lesion, when it can be accomplished safely, is suggested over observation or lesser extent of resection/biopsy to improve seizure control.

New Recommendations

Level III: It is suggested that extent of resection be maximized as is safely possible for isocitrate dehydrogenase (IDH) mutant and isocitrate dehydrogenase wild type WHO grade II diffuse gliomas to improve progression free survival (PFS) and OS.

Level III: There is insufficient evidence that greater extent of resection of 1p19q codeleted oligodendrogliomas (WHO grade II diffuse gliomas) improves OS.

Level III: The use of intraoperative ultrasound is suggested to increase the extent of resection compared with conventional surgery for adults with WHO grade II diffuse glioma.

Level III: Intraoperative fluorescent-guided surgery with 5-aminolevulinic acid is not suggested to improve the extent of resection for WHO grade II gliomas.

Level III: It is suggested that awake craniotomy and other methods of intraoperative mapping can be used to increase the extent of resection for adults with WHO grade II diffuse glioma.

Level III: The use of functional MRI and diffusion tensor imaging–related modalities are suggested to decrease surgical morbidity in adults with WHO grade II diffuse glioma.

Pathology

Unchanged Recommendations from the Prior Version of These Guidelines

Level I: Histopathological analysis of a representative surgical sample of the lesion should be used to provide the diagnosis of low-grade diffuse glioma.

Level III: Both frozen section and cytopathological/smear evaluation should be used to aid the intraoperative assessment of low-grade diffuse glioma diagnosis. A resection specimen is preferred over a biopsy specimen to minimize the potential for sampling error issues.

Level II: IDH gene mutation assessment, through IDH1 R132H antibody and/or IDH1/2 mutation hotspot sequencing, is highly-specific for low-grade diffuse glioma and is recommended as an additional test for classification and prognosis.

Level III: 1p/19q loss-of-heterozygosity testing, by fluorescence in situ hybridization, array-comparative genomic hybridization or polymerase chain reaction, is recommended as an additional test in oligodendroglial cases for prognosis and potential treatment planning.

There is insufficient evidence to recommend methyl-guanine methyl-transferase promoter methylation testing as a routine for low-grade diffuse gliomas. It is recommended that patients be enrolled in properly designed clinical trials to assess the value of this and related markers for this target population.

Level III: Ki67/E3 ubiquitin-protein ligase Mind Bomb 1 immunohistochemistry is recommended as an option for prognostic assessment.

New Recommendations

There is insufficient evidence to recommend alpha-thalassemia/mental retardation X-linked mutation testing as a means of predicting survival or making treatment recommendations.

There is insufficient evidence at this time to suggest that intraoperative optical histological methods offer increased diagnostic accuracy when compared with conventional techniques.

Chemotherapy

Recommendations from the Prior Version of These Guidelines Without Change

Level III: Chemotherapy is recommended as a treatment option to postpone the use of radiotherapy to slow tumor growth and to improve PFS, OS and clinical symptoms in adult patients with newly diagnosed LGG.

Level III: Chemotherapy is recommended as an optional component alone or in combination with radiation as the initial adjuvant therapy for all patients who cannot undergo gross total resection of a newly diagnosed LGG. The patient with residual tumor (1 cm on postoperative MRI) presenting diameter of 4 cm or older than 40 years should be considered for adjuvant therapy as well.

Level III: The addition of chemotherapy to standard radiation therapy (RT) is recommended in LGG patients who carry IDH mutation. In addition, temozolomide is recommended as a treatment option to slow tumor growth in patients who harbor the 1p/19q codeletion.

There is insufficient evidence to make a definitive recommendation on the timing of starting chemotherapy after surgical/pathological diagnosis of LGG has been made. However, using the 12 weeks mark as the latest timeframe to start adjuvant chemotherapy is suggested. It is recommended that patients be enrolled in properly designed clinical trials to assess the timing of chemotherapy initiation once diagnosis is confirmed for this target population.

There is insufficient evidence to make a recommendation of one particular regimen. Enrollment of subjects in properly designed trials comparing the efficacy of these or other agents is recommended so as to determine which of these regimens is superior.

Insufficient evidence exists regarding the duration of any specific cytotoxic drug regimen for treatment of newly diagnosed LGG. Enrollment of subjects in properly designed clinical investigations assessing the optimal duration of this therapy is recommended.

Insufficient evidence exists to make recommendations in this regard. Hence, enrollment of patients in properly designed clinical trials assessing the difference between chemotherapy alone, RT alone, or a combination of them is recommended.

Level II: It is recommended that chemotherapy be added to the RT in patients with unfavorable LGG to improve their progression free survival.

Updated Question and Recommendations from the Prior Version of These Guidelines

Level I: It is recommended that chemotherapy (procarbazine) be added to RT in all patients with newly diagnosed high-risk WHO grade II diffuse glioma (patients younger than 40 years unable to get gross total resection and older than 40 years regardless of the degree of resection) to improve their overall survival.

Level II: It is recommended that chemotherapy be added to radiation therapy in all patients with newly diagnosed high-risk WHO grade II diffuse glioma to improve overall survival without a decline in neurocognitive function.

Level III: It is recommended that chemotherapy (temozolomide) be added to RT in all patients with newly diagnosed high-risk WHO grade II diffuse glioma to improve progression free survival and overall survival.

Level III: It is suggested that chemotherapy alone should be considered in patients with newly diagnosed WHO grade II diffuse glioma in cases with 1p/19q codeletion.

New Recommendations

Level III: Neo-adjuvant temozolomide may be used in patients with WHO grade II diffuse gliomas deemed unsafe for resection due to infiltration of eloquent areas or with large contralateral extension as an initial step to improve the extent of resection.

There is insufficient evidence to support a recommendation regarding the ability of chemotherapy provided before surgical resection to improve PFS and OS.

There is insufficient evidence to support a recommendation against the use of temozolomide for WHO grade II diffuse gliomas due to concern over increasing the rate of malignant transformation.

There is insufficient evidence to support a recommendation for or against the use of multiagent chemotherapy to improve progression free survival and overall survival when compared with administration of single-agent chemotherapy in patients with newly diagnosed WHO grade II diffuse glioma.

Radiation Therapy

Questions and Recommendations from the Prior Version of These Guidelines Without Change

Level I: Radiotherapy is recommended in the management of newly diagnosed low-grade glioma in adults to prolong progression-free survival, irrespective of extent of resection.

Level II: Radiotherapy is recommended in the management of newly diagnosed low-grade glioma in adults as an equivalent alternative to observation in preserving cognitive function, irrespective of extent of resection.

Level III: Radiotherapy is recommended in the management of newly diagnosed low-grade glioma in adults to improve seizure control in patients with epilepsy and subtotal resection.

Level III: Radiotherapy is recommended in the management of newly diagnosed low-grade glioma in adults to prolong overall survival in patients with subtotal resection.

Level III: Consideration of the risk of radiation induced morbidity, including cognitive decline, imaging abnormalities, metabolic dysfunction, and malignant transformation, is recommended when the delivery of radiotherapy is selected in the management of newly diagnosed low-grade glioma in adults.

Level I: Lower-dose radiotherapy is recommended as an equivalent alternative to higher dose immediate postoperative radiotherapy (45-50.4 vs 59.4-64.8 Gy) in the management of newly diagnosed low-grade glioma in adults with reduced toxicity.

Level III: Delaying radiotherapy until recurrence or progression is recommended as an equivalent alternative to immediate postoperative radiotherapy in the management of newly diagnosed low-grade glioma in adults but may result in shorter time to progression.

Level III: The addition of chemotherapy to radiotherapy is not recommended over whole brain radiotherapy alone in the management of low-grade glioma, as it provides no additional survival benefit.

Level III: Limited-field radiotherapy is recommended over whole brain radiotherapy in the management of low-grade glioma.

Level III: Either stereotactic radiosurgery or brachytherapy is recommended as acceptable alternatives to external radiotherapy in selected patients.

Level II: It is recommended that age older than 40 years, astrocytic pathology, diameter greater than 6 cm, tumor crossing the midline, and preoperative neurological deficit be considered as negative prognostic indicators when predicting overall survival in adult low-grade glioma patients treated with radiotherapy.

Level II: It is recommended that smaller tumor size, extent of surgical resection and higher mini-mental status examination be considered as positive prognostic indicators when predicting overall survival and progression-free survival in patients in adult low-grade glioma patients treated with radiotherapy.

Level III: It is recommended that seizures at presentation, presence of oligodendroglial histological component, and 1p19q deletion (along with additional relevant factors—see evidence tables) be considered as positive prognostic indicators when predicting response to radiotherapy in adults with low-grade gliomas.

Level III: It is recommended that increasing age, decreasing performance status, decreasing cognition, and presence of astrocytic histological component (along with additional relevant factors [see evidence tables]) be considered as negative prognostic indicators when predicting response to radiotherapy.

New Recommendations

There is insufficient evidence to provide guidance on the superiority or inferiority of proton radiation effect compared with standard radiation therapy on WHO grade 2 diffuse glioma for overall survival, progression-free survival, local control, complications, neurocognitive preservation, and quality of life.

Level III: It is suggested that 1p/19q deletion status be used as a positive prognostic indicator regarding the effect of radiation therapy on progression free survival and overall survival for WHO grade II diffuse gliomas.

Recurrence

Unchanged Recommendations from the Prior Version of These Guidelines

Imaging

Level III: In adult patients with suspected recurrence of histologically proven WHO grade 2 diffuse glioma, advanced imaging techniques using magnetic resonance spectroscopy, perfusion-weighted imaging, diffusion-weighted imaging, or PET are suggested for identification of tumor recurrence or histological progression.

Pathology

Level III: It is suggested that IDH mutation status be determined for diagnostic purposes. TP53 mutations occur early in WHO grade 2 diffuse glioma pathogenesis, remain stable, and are not suggested as a marker of predisposition to malignant transformation at recurrence or other measures of prognosis. Assessment

of methyl-guanine methyl-transferase status is suggested as an adjunct to assessing prognosis.

Level III: It is suggested that proliferative indices (E3 ubiquitin-protein ligase Mind Bomb 1 or bromodeoxyuridine) be measured in WHO grade 2 diffuse glioma as higher proliferation indices are associated with increased likelihood of recurrence and shorter progression-free and overall survival.

Chemotherapy

Level III: Temozolomide is suggested in the therapy of recurrent WHO grade 2 diffuse gliomas as it may improve clinical symptoms. Procarbazine is suggested in the therapy of WHO grade 2 diffuse gliomas at recurrence as it may improve clinical symptoms with the strongest evidence being for oligodendrogliomas. Temozolomide is suggested as the initial choice for recurrent WHO grade 2 diffuse gliomas. Carboplatin is not suggested as there is no significant benefit from carboplatin as single agent therapy for recurrent WHO grade 2 diffuse gliomas. There is insufficient evidence to make any recommendations regarding other agents in the management of recurrent WHO grade 2 diffuse gliomas.

Radiotherapy

Level III: Radiation is suggested at recurrence if there was no previous radiation treatment.

Level III: It is suggested that reirradiation be considered in the setting of WHO grade 2 diffuse glioma recurrence as it may provide benefit in PFS and OS.

Surgery

There is insufficient evidence to make any new specific recommendations regarding the value of surgery or extent of resection in relationship to survival for recurrent WHO grade 2 diffuse gliomas.

INTRODUCTION

Goals and Rationale

The guidelines for the management of low-grade gliomas was sponsored by the Congress of Neurological Surgeons (CNS) and endorsed by the American Association of Neurological Surgeons (AANS) and CNS were published in 2015.[1-9] As suggested by the Institute of Medicine, now the National Academy of Medicine, it is suggested that guidelines be updated in the range of every 5 years.[10] That interval allows for a reasonable time to assess new methods of diagnosis and treatment including imaging, surgical approaches, neuropathology and molecular markers, radiation, chemotherapy, and management of recurrent tumors that have developed since the time of the publication in 2015.[11-18]

As before, these guidelines are presented as a set of documents separated by management topic to look at the role of imaging, surgical approaches, neuropathology and molecular markers, radiation therapy, chemotherapy, and recurrent tumors.[19-23] They are produced using the evidence-based methodology supported by the Joint Guidelines Review Committee of the AANS and CNS.

Objectives and Guideline Panel Development

The overall objective of this series of guideline documents is to confirm or update the previous evidence-based recommendations for the management of patients with low grade gliomas, now more accurately referred to as WHO grade II diffuse gliomas, centering on questions related to the most commonly used diagnostic and treatment modalities. The primary consequence of this work will ideally be to point out the current state of knowledge about the management of this disease process and serve as a point of departure for the development of diagnostic and treatment improvements for patients with this diagnosis.

METHODOLOGY

Topical Range of the Systematic Review and Clinical Practice Guidelines

The questions to be answered about the treatment of WHO grade II diffuse gliomas were determined by the clinical panel. These questions and subsequent recommendations are presented at the beginning of each guideline section of which there are 6 in all. This includes questions about imaging, surgical approaches, neuropathology and molecular markers, radiation therapy, chemotherapy, and recurrent tumors.

Literature Search

A broad literature search strategy was undertaken to identify all citations relevant to the management of WHO grade II diffuse gliomas. The MEDLINE and Embase electronic databases and the Cochrane Database of Systematic Reviews were searched from January 1, 2013, through January 31, 2020, using the search strategies provided.

Rating Quality of Evidence

The quality of evidence was rated using an evidence hierarchy for each of 4 different study types: therapeutic, prognostic, diagnostic, and decision modeling (https://www.cns.org/guidelines/low-grade-glioma/low-grade-glioma-guideline-update). Additional information regarding the hierarchy classification of evidence is located at https://www.cns.org/guidelines/guideline-development-methodology.

Guideline Panel Consensus and Practice Guideline Approval Process

The completed updates of the evidence-based clinical practice guidelines on the management of progressive glioblastoma were presented to the Joint Guidelines Review Committee of the AANS/CNS to assess methodology, content, and conclusions. The reviewers for the Joint Guidelines Review Committee were vetted by Neurosurgery for suitability and expertise to serve as reviewers for the purposes of publication in that journal also.

Figure presents an outline of the key steps in the process of developing these clinical practice guidelines.

Revision Plans

In accordance with the Institute of Medicine's standards for developing clinical practice guidelines and criteria specified by the National Guideline Clearinghouse, the task force will monitor related publications after the release of this document and will revise the entire document and/or specific sections "if new evidence shows that a recommended intervention causes previously unknown substantial harm; that a new intervention is significantly superior to a previously recommended intervention from an efficacy or harms perspective; or that a recommendation can be applied to new populations."[1] In addition, the task force will confirm within 5 years from the date of publication that the content reflects current clinical practice and the available technologies for the evaluation and treatment for patients with LGG.

DISCUSSION

This series of guideline documents were constructed primarily to update the currently existing evidence for management of WHO grade II diffuse gliomas in a manner that sets a benchmark for further improvement in this task. By designing future investigations to provide high-quality evidence overcoming prior weaknesses and limitations, noted in these guidelines, advancement toward a remedy of this disease will be achieved. Fortunately, new research results are constantly coming to light and these guidelines are meant to be updated in 5 years with earlier updates should new important, practice changing, evidence be published.

Conflict of Interest

All Guideline Task Force members were required to disclose all potential COIs before beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee. The CNS Guidelines Committee and

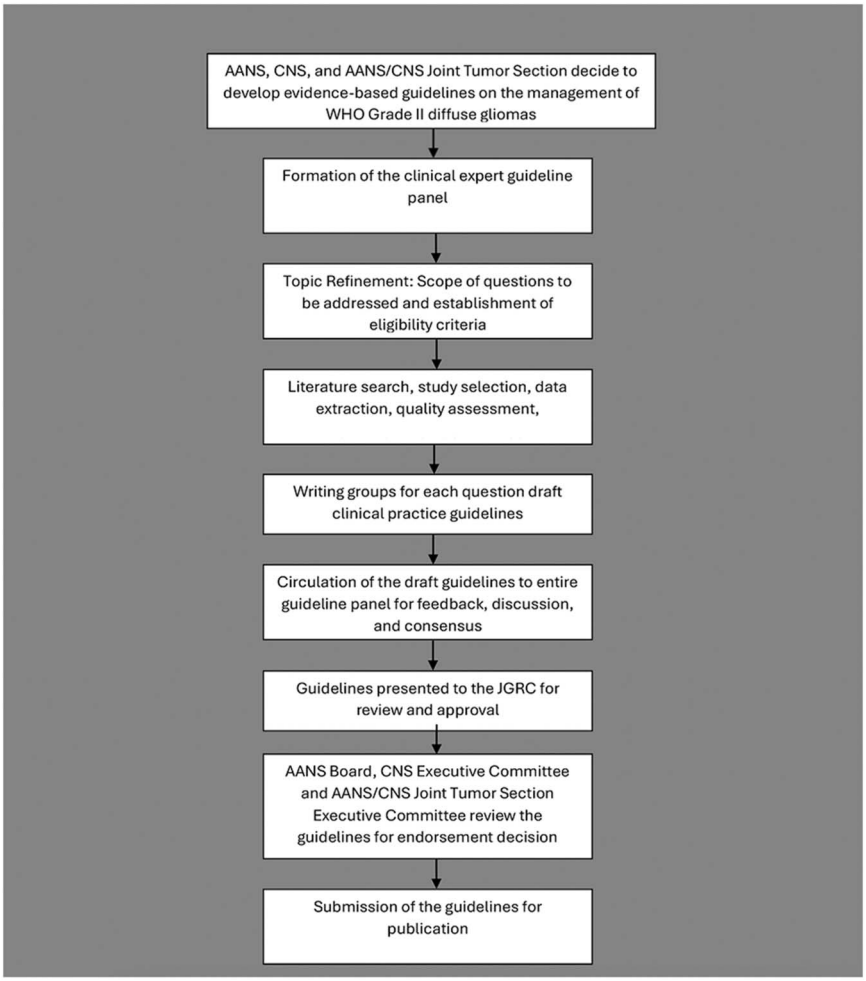

FIGURE. *Overview of the guideline development process. AANS, American Association of Neurological Surgeons; CNS, Congress of Neurological Surgeons; JGRC, Joint Guidelines Review Committee; WHO, World Health Organization.*

TABLE. Conflict of Interest Disclosures

D. Ryan Ormond	DePuy Synthes, Longeviti, Servier BioInnovation, Merck Sharp & Dohme LLC, Integra LifeSciences Corporation
Chaitra Badve	Siemens Medical Solutions USA
Navid Redjal	Telix Pharmaceuticals
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Mateo Ziu	Stryker Corporation, Zap Surgical Systems, Zimmer Biomet Holdings
Jeffrey J. Olson	Azurity Pharmaceuticals Verastem, Inc.

Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs. See Table for a complete list of disclosures.

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article except those noted in the table above.

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