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Guidelines for the Diagnosis and Clinical Management of Cavernous Malformations of the Brain and Spinal Cord: Consensus Recommendations Based on a Systematic Literature Review by the Alliance to Cure Cavernous Malformation Clinical Advisory Board Experts Panel

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BACKGROUND AND OBJECTIVES: Despite many publications about cavernous malformations (CMs), controversy remains regarding diagnostic and management strategies. To update evidence-based guidelines for the clinical management of brain and spinal cord CMs.

METHODS: The Alliance to Cure CMs, the patient support group in the United States advocating on behalf of patients and research in CM, convened a multidisciplinary writing group comprising expert CM clinicians to help summarize the existing literature related to the clinical care of CM, focusing on 5 topics: (1) epidemiology and natural history, (2) genetic testing and counseling, (3) diagnostic criteria and imaging standards, (4) neurosurgical considerations, and (5) neurological considerations. Building on prior evidence-based recommendations reflecting literature review through October 2014, the group conducted a systematic review of the more recent literature, identified references for mandatory citation, rated evidence, developed recommendations, and established consensus according to a prespecified protocol. Finally, the writing group outlined remaining knowledge gaps and controversies to guide future research.

ABBREVIATIONS: 25-OH Vit D, 25-hydroxy vitamin D; **ASM,** antiseizure medication; **CMs,** cavernous malformations; **CRE,** CM-related epilepsy; **DVA,** developmental venous anomaly; **FCM,** familial cavernous malformations; **FND,** focal neurological deficits; **LITT,** interstitial thermal ablation; **Spinal CM,** Spinal Cord CM; **SRS,** stereotactic radiosurgery; **TLR-4,** Toll-like receptor 4.

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RESULTS: From 2672 publications published between October 1, 2014, and March 15, 2023, and meeting key word criteria, 234 were selected based on prearticulated criteria for mandatory consideration in evidence-based recommendations. Topic authors used these and other supporting references to summarize current knowledge and arrive at 53 management recommendations, with unanimous consensus based on a Delphi process. These were rated by class (strength of recommendation) and level (quality of evidence) per the American Heart Association/American Stroke Association criteria. Eighteen recommendations were class 1 (34%), class 2 in 31 (58%), and class 3 in 4 (8%). Three were level A (6%), 19 (36%) were level B, and 31 (58%) were level C.

CONCLUSION: Current evidence supports prior and new recommendations for the management of CMs, but many reflect moderate classes and low levels, mandating further research to better inform clinical practice.

KEY WORDS: Angioma, Cavernoma, Cavernous, Guidelines, Malformation, Recommendations

Cavernous malformation (CM) is also referred to in the literature as cavernous angioma, hemangioma, or cavernoma (Online Mendelian Inheritance in Man (OMIM) #116860). It comprises closely clustered, abnormally dilated and leaky capillary caverns that occur in the central nervous system parenchyma. Previous evidence-based guidelines for clinical management were articulated by the Alliance to Cure CMs (www.alliancetocure.org, formerly known as Angioma Alliance) in 2017,[1] based on a systematic literature review through October 2014 (**Supplemental Digital Content 1** [http://links.lww.com/NEU/E735]). Since then, many articles have been published in the peer-reviewed literature including new information about natural history and genetics, novel imaging, surgical techniques and outcomes, and medical management. In addition, the prior recommendations did not offer explicit diagnostic guidelines, address spinal cord lesions specifically, pediatric cases, or those in older people. We hence undertook this task of reviewing and updating prior recommendations.

METHODS

As with the prior guidelines, a multidisciplinary writing group ("Writing Group"), including members of the Alliance to Cure CMs Clinical Advisory Board and invited experts, was assembled to help summarize the existing literature related to the clinical care of CM, focusing on 5 key topics: (1) epidemiology and natural history, (2) genetic testing and counseling, (3) diagnostic criteria and imaging standards, (4) neurosurgical considerations, and (5) neurological considerations. For each topic, specific questions were formulated by the writing group with input from the Alliance to Cure patient community, and these were developed into a proposed outline of the sections addressing the 5 key topics and were used to generate specific key words for the literature search. Members of the Writing Group were assigned to each of the 5 respective topics ("Topic Authors") based on their areas of expertise, each with a lead topic author. Search terms and criteria of systematic literature review, cataloging of selected references, assignments to topic writing groups, and the Delphi process of consensus generation[2] are summarized in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735). We used the current criteria for classes (strength of recommendation) and level (quality) of evidence by the American Heart Association/American Stroke Association.[3] Class 1 recommendations are strong with the benefit outweighing the risk, class 2 recommendations have less benefit, while class 3 recommendations are those in which risk and benefit are relatively equal. The quality of evidence is ranked from A (highest) through C (lowest) with the following abbreviations: (R) Randomized, (NR) Nonrandomized, (LD) Limited Data, and (EO) Expert Opinion.[3] There was no attempt in these guidelines to assess the potential bias in individual studies or across studies nor the impact that bias might have on the recommended guidelines.

EPIDEMIOLOGY AND UNTREATED CLINICAL COURSE

Disease Prevalence and Incidence

CMs can occur sporadically or as part of a disorder called familial CM (FCM). CMs are common, with a prevalence of 0.16% based on incidental MRI findings,[4] and as high as 0.5% based on autopsy studies,[5] with increasing prevalence of detection at older ages.[6] The population-based annual detection rate of CM was estimated at 0.56 per 100 000 per year for adults older than 16 years in Scotland in the 2000s,[7] but it is likely to be higher now with the greater availability and uptake of MRI. The population prevalence and detection rate of spinal (intramedullary and nerve root) CMs are unknown, but their prevalence among intramedullary CMs detected at tertiary referral centers is believed to be ~5% in adults and ~1% in children.[8,9]

People with CM present with a broad range of symptoms typically in the second to fifth decade of life. The most common clinical manifestations of CM include seizures (50%) and stroke due to intracranial hemorrhage (ICH) (25%) or new focal neurological deficits (FND) without radiographic evidence of recent hemorrhage (25%).[10] Spinal Cord CM (Spinal CM) tends to present with sudden and often step-wise or slowly progressive[11] radiculopathies or myelopathies causing weakness or sensory disturbance in the arms and/or legs, pain, and sphincter disturbance, according to their location; 4 types of presentation have been classified by Ogilvy.[12] Many CMs are discovered incidentally due to widespread availability and use of brain MRI for investigation of symptoms that turn out to be unrelated to CM or for screening.[4,13]

Familial and Sporadic Forms of CM

CMs can occur in either a sporadic or familial form or after radiation therapy.[14] Most cases are sporadic with no family history

and typically present as a single CM, with or without an associated developmental venous anomaly (DVA). Approximately 20% of cases present with multiple CMs,[10,15] many with a positive family history (ie, relatives with symptomatic or asymptomatic CM on MRI) consistent with autosomal dominant inheritance, and the presence of lesions in other organs (eg, skin and retina). The diagnosis of familial CM can be confirmed by genetic testing for mutations in 3 genes: *CCM1* (*KRIT1*), *CCM2* (*MGC4607*), or *CCM3* (*PDCD10*) (see genetic testing section for more details). CM has been reported in all races/ethnicities; however, 3 founder mutations exist in the US population, increasing risk in these subgroups. Hispanics who share a 400-year history in the Southwest region of the United States and northern states of Mexico have a higher prevalence of FCM[16,17] due to a founder mutation in *CCM1* (Q455X or "Common Hispanic Mutation"). The founder mutation explains the majority of cases in this geographically specific ethnic group.[18,19] A founder mutation of *CCM2* (c.30+5_30_6delinsTT) has been identified in Ashkenazi Jewish patients in the United States,[20] with cases in many major metropolitan areas. A third founder mutation, a large deletion of exons 2-10 of the *CCM2* gene and neighboring *NACAD* gene ("CCM2 Exon 2-10 Deletion"), has been found in at least 50 unrelated White families that trace their heritage to the 1700s Southeastern United States.[21] This subgroup has since dispersed but is still found in higher concentration in states considered part of the American Deep South.

Natural History (Untreated Clinical Course)

Definition of Hemorrhage and Hemorrhage Rates

Symptomatic ICH is the most feared complication of CM, and its prevention is one of the main indications for treatment. CM symptomatic ICH was standardized in 2008 as "requiring acute or subacute onset symptoms (any of: headache, epileptic seizure, impaired consciousness, or new/worsened FND referable to the anatomic location of the CM) accompanied by radiological, pathological, surgical, or rarely only cerebrospinal fluid evidence of recent extralesional or intralesional hemorrhage."[22] Other information on natural history is presented in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

Cerebral CMs

We updated a systematic review of studies published since 2017[1] that (1) included 20 or more people with CM, (2) presented annual ICH rates per-person year of follow-up after diagnostic presentation, (3) had at least 1 year of follow-up, and (4) were published in the English language. In studies with no selection criteria or with at least 1 large CM (≥5 mm), the annual ICH rate per person-year ranged from 0.7% to 7.5% overall,[17,23-32] 0.2% to 4.9% for first ICH,[10,13,15,29-36] and 1.7% to 29.5% for a second ICH.[13,17,28-30,32-38] A small case series of 42 people with a recurrent CM ICH found that the risk of a third ICH was 66.7% (95% CI 50%-80%) over 5 years, which seems significantly higher than the risks of first and second ICH.[37] All studies reported higher rates for recurrent ICH than first ICH. Several meta-analysis studies have been conducted: one used aggregate data from published studies[38] and another used individual patient data from 7 cohorts reporting a 5-year cumulative ICH risk of 15.8% (13.7%-17.9%) overall.[39] Pooling results from 7 studies with over 5081 person-years of follow-up, the annual ICH rate was 2.5% (1.3%-5.1%) per person-year.[38] Three studies and the individual patient data meta-analysis also showed that the annual risk of ICH significantly declined over up to 5 years of follow-up,[10,15,39] which has long-term clinical implications when weighing treatment decisions for people with CM. Furthermore, the risk of first ICH was very low (0.08% per person-year) among CM cases identified incidentally.[13]

Spinal CMs

Data available on the rates of hemorrhage in the untreated clinical course of spinal CM are sparse and even more susceptible to selection bias and confounding than CM because of the tendency to treat neurological symptoms due to spinal CM, as well as the same methodological problems described for CM above.

Familial Risk of Bleeding

The presence of multiple CMs may cause a higher hemorrhage risk in familial cases. However, recent individual patient data meta-analysis of prognosis did not confirm this hypothesis,[39] and bleed risk may also differ depending on the causative gene mutation. Higher annual ICH rates per patient-year are seen in FCM cases compared with sporadic cases (4.3%-16.5%).[1,17,32,35,40,41]

In particular, *CCM3* mutation carriers are more likely to present with an ICH at an earlier age compared with *CCM1* and *CCM2* patients.[1] ICH rates per patient-year in 18 *CCM3* cases of 20% (95% CI 14%-28%) were reported since onset of symptoms and 24% (95% CI: 16%-35%) for recurrent hemorrhage.[1] Correlation with CM count revealed that the annual risk of hemorrhage per CM (0.3%, 95% CI 0.2%-0.4%) is similar to other genotypes, indicating that the higher hemorrhage risk in *CCM3* cases was largely due to greater CM burden. Greater CM burden at baseline enrollment in a primarily *CCM1* cohort was also found to be a significant predictor of subsequent ICH during follow-up, independent of prior ICH (hazard ratio = 1.37 per doubling of total CM count, 95% CI 1.10-1.71).[41]

Seizures

Seizures related to CM are believed to be induced by a first symptomatic hemorrhage or by recurrent microhemorrhages, resulting in surrounding blood (hemosiderin), perilesional gliosis, and inflammation.[42] Josephson et al[43] performed a prospective population-based study of 139 adults diagnosed with CM and found a 5-year risk of first-ever seizure was 6% (95% CI 0%-14%) in 38 CM patients presenting with ICH/FND and 4% (95% CI 0%-10%) in 57 CM patients presenting incidentally. Among adults who never experienced ICH/FND and presented with or developed epilepsy, the proportion achieving 2-year seizure freedom over 5 years was 47% (95% CI 27%-67%). Similarly,

among 38 patients with a single supratentorial CM undergoing conservative management for new-onset epilepsy, 32% remained seizure-free at 2 years.[44] Among 479 FCM patients followed prospectively, the cumulative incidence of first-ever seizure was 20% by age 18 years (95% CI 17%-23%) and 60% by age 80 years (95% CI 54%-66%).[45] FCM patients with seizures before enrollment had significantly increased risk of hospitalization rates during follow-up compared to those without seizures.[45] A meta-analysis of 5 studies found similar seizure rates in familial and nonfamilial CM cases with a pooled incidence rate of 1.5% per patient-year (95% CI 1.1%-2.2%).[46]

Functional Outcome

Many different measures are used to assess functional status and disability in patients. Most stroke clinical trials use the modified Rankin Scale (mRS) score as a measure of global disability.[47] However, the mRS has several known limitations, including high interobserver variability, stacking of scores at the high or low end of distribution (eg, floor and ceiling effects), focus on physical function, and the lack of communication or cognition assessment.[48,49] Thus, recent CM studies have also estimated patient-reported outcomes using generic health-related quality of life (QoL) surveys, eg, the short-form-36 questionnaire,[50-52] the hospital and anxiety and depression score (A/D),[51,52] and the Patient-Reported Outcomes Measurement Information System.[53,54] In general, all studies reported worse outcomes in CM patients compared with a general reference population on domains assessed. In particular, anxiety is frequently reported by patients as significantly affected by CM disease.[48-54] There is no standardized tool for assessing outcome in CM studies, and many derivatives of the mRS exist, such as the Oxford Handicap Scale, which has been used in some CM studies.[55]

GENETIC TESTING AND COUNSELING

FCM can be diagnosed *clinically* through the occurrence of either of the following 2 scenarios: (1) an individual with multifocal noncontiguous cerebral CMs generally not closely associated around a DVA or (2) an individual with a CM who has at least one additional family member with CM.[56] Among all cases of CMs, approximately 80% are sporadic and approximately 20% are FCM. However, these estimates may be confounded by the fact that each of the genetic causes of FCM (see below) can be associated with incomplete penetrance and variable testing and expressivity even within families.

FCM Genes

A molecular diagnosis of FCM in an individual occurs through detection of a heterozygous, loss of function, pathogenic, or likely pathogenic germline variant in 1 of 3 genes: *KRIT1* (*CCM1*), *CCM2*, and *PDCD10* (*CCM3*).[1,57] The functions of these genes continue to be investigated; all are involved in signaling networks responsible for the maintenance of junctional integrity between neighboring vascular endothelial cells.[58] The mode of inheritance for each of these 3 genetic disorders is autosomal dominant. The penetrance of all 3 FCM mutation-related diseases is incomplete and dependent on age. Penetrance is greater in adults and when using susceptibility-weighted imaging (SWI) sequences and higher magnetic strength for MRI diagnosis.

Mechanisms of familial CM disease, diagnostic yield and variants, gene phenotype correlations, and recent discoveries related to somatic mutations in CM lesions are further summarized in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

Recommendations for Testing

For individuals who meet clinical criteria for FCM, for whom the CMs are not associated with focal brain radiation nor are they clustered in association with a DVA, genetic testing should include full gene sequencing of *KRIT1* (*CCM1*), *CCM2*, and *PDCD10* (*CCM3*) including assays for deletion/duplication analysis.[1] A founder mutation, termed the Common Hispanic Mutation, on the *CCM1* gene commonly occurs in individuals of Hispanic ancestry of Mexican descent and/or those descending from the original Spanish settlers of the American southwest. Those with CM diagnosis and this ancestry should first be tested first for the Common Hispanic Mutation, *CCM1* c.1363C>T; p.Q455X and, if this is not detected, should then proceed to testing of the other 3 genes as above. Although targeted testing for the CCM2 Ashkenazi Jewish founder mutation and the CCM2 Exon 2-10 deletion founder mutation is available, at this time, there is not a compelling reason to test these first. The results of genetic testing can be used in decisions about medical management, especially in the setting of increased disease severity associated with *CCM3* variants.

For asymptomatic but at-risk family members of probands with molecularly confirmed FCM, genetic testing is the best way to screen for FCM, with some ethical caveats. Given the high incidence of asymptomatic individuals with a pathogenic/likely pathogenic variant in a FCM-related gene, the absence of symptoms in a family member cannot definitely exclude the diagnosis of FCM in the setting of a known familial pathogenic/likely pathogenic variant.[59] Genetic testing is a cost-effective and noninvasive tool for screening both symptomatic and asymptomatic family members. Genetic testing of asymptomatic at-risk individuals (particularly children) could raise possible ethical concerns. On one hand, currently there is no preventive or curative therapy for those testing positive, but on the other hand, genetic confirmation of FCM may lower the threshold for neuroimaging when neurological symptoms arise. Moreover, in cases of FCM with a known familial mutation, genetic testing can rule out diagnosis without the need for neuroimaging. Consultation with a genetic specialist is recommended before screening asymptomatic at-risk individuals. Prenatal and preimplantation genetic diagnosis is also available for interested individuals and

families with a known pathogenic/likely pathogenic variant. A summary of these recommendations is listed in Table 1.

IMAGING CONSIDERATIONS

Imaging Techniques

Imaging is key to the diagnosis and evaluation of CMs.[1] Many asymptomatic CMs are incidentally identified on imaging studies performed for reasons unrelated to the CM. Since computerized tomography (CT) scan is often the initial neuroimaging study performed for many emergent neurological symptoms, some larger CMs may initially be identified on CT. The appearance of CMs on CT as hyperattenuation and sometimes calcification is somewhat nonspecific and would overlap with other intracranial mass lesions, calcifications, and hemorrhage. CT is also insensitive to the detection of smaller CMs and intralesional hemorrhage. Nonetheless, CT remains an important diagnostic tool for neurological emergencies and is often the first-line study conducted for the evaluation of possible ICH or infarction. Identification of a lesion that may possibly be a CM on CT would often require follow-up MRI for further evaluation. MRI remains the preferred imaging test for the confirmation, detection, and evaluation of CMs and suspected bleeding.[1]

The most typical appearance is "popcorn" appearance on T2 and fluid-attenuated inversion recovery sequences, reflecting blood of different ages in the cavernous spaces, surrounded by a "hemosiderin ring" of T2 hypointense signal. Acute bleeding in or near the lesions is best seen on T1 sequences and may distort this typical appearance; a repeat MRI after the acute blood has resolved will usually reveal an underlying typical "popcorn" appearance lesion with a hemosiderin ring.

Very small CMs are only seen as foci of susceptibility signal on SWI or other similar hemosiderin-sensitive imaging sequences. The imaging appearance of these small CMs thus overlaps with other causes of susceptibility signal including prior microhemorrhages from a variety of causes, such as hypertensive hemorrhages, trauma, amyloid angiopathy, radiation therapy-related, hemorrhagic metastases, or any other cause of hemorrhage, and with calcifications which could be the result of infection or other nonspecific dystrophic calcifications. In addition to the appearance on SWI or similar imaging, many CMs will have a more specific MRI appearance on T1-weighted and T2-weighted imaging including the classic "popcorn" or "mulberry" appearance CM with a T2 hypointense rim of susceptibility signal ("hemosiderin ring") and a more complex internal heterogenous reticulated appearance, CMs characterized only by susceptibility signal (hypointense hemosiderin signal on T2-weighted and T1-weighted imaging), and CMs in which the center is completely T1 hyperintense.[60]

Vascular imaging is often performed in the evaluation of potential ischemic or hemorrhagic stroke and thus may be performed in patients who present acutely. This can include CT angiogram, which is often performed out of the emergency room for suspected stroke, magnetic resonance angiogram, and, in some cases, invasive catheter angiography. Although it may be possible to see CMs and associated DVAs on these studies, their role in the evaluation of CMs is limited and would mostly be used to evaluate for other conditions such as arterial occlusion, aneurysm, arteriovenous malformation, or shunting.

Diagnosis and Differential Considerations

Imaging should focus on making the diagnosis of CM, identifying multiple CMs that would suggest a genetic cause, and identifying imaging findings of recent hemorrhage including any edema in the surrounding brain parenchyma. Identifying an associated DVA can be an important surgical consideration and can help make the diagnosis of a CM given the frequent association especially with sporadic CMs.[61] Larger CMs are often readily recognized on MRI given their characteristic appearance

TABLE 1. Recommendations Regarding Genetic Testing

Recommendation	Level of evidence
1. A 3-generation family history is useful at the time of a new diagnosis, focusing on symptoms of headache, stroke, seizures/epilepsy, abnormal MRI scan, neurodevelopmental impairment, or other neurological complications.	Class 1, Level C-EO
2. In the setting of FCM, or multiple CMs without an associated DVA or prior brain radiation, it can be beneficial to consider genetic testing of *KRIT1*, *CCM2*, and *PDCD10* genes by Sanger or NextGen sequencing as well as deletion/duplication analysis.	Class 2a, Level B-NR
3. In the setting of a pathogenic/likely pathogenic variant in *KRIT1*, *CCM2*, or *PDCD10* in a proband, the individual and family should be counseled about autosomal dominant inheritance and identify at-risk individuals based on the pedigree.	Class 1, Level C-EO
4. Genetic testing of at-risk family members can be useful to guide healthcare decisions, and consultation with a genetic specialist is recommended before screening asymptomatic at-risk individuals.	Class 2a, Level C-EO
5. Asymptomatic at-risk family members should be provided with information by a genetic specialist on the possible psychological consequences of a diagnostic test before they make their decision.	Class 1, Level C-EO

CM, cavernous malformation; DVA, developmental venous anomaly; EO, expert opinion; FCM, familial cavernous malformations; NR, nonrandomized.

(especially CMs with the classic "popcorn" or "mulberry" appearance with peripheral susceptibility signal). Sometimes, however, there is a diagnostic dilemma, and differential considerations must be considered given the overlap in appearance with other hemorrhagic and/or calcified lesions. A recent bleed with focal hematoma may potentially obscure an underlying CM, hemorrhagic mass, other vascular malformation such as a small arteriovenous malformation, or in some cases may resemble a CM when one does not exist. Non-CM hemorrhagic lesions may also manifest blood-like high T1 signal on MRI.[62] In such cases, follow-up imaging studies would be helpful to evaluate the appearance/evolution of the hematoma/hemorrhagic lesion over time and come to an ultimate diagnosis.

MRI with recommended sequences (Table 2) should be performed in patients who carry a familial mutation. This investigates nonspecific neurological symptoms and provides a baseline CM burden for future follow-up.[1,63] Some cases with a CCM gene mutation may have negative MRIs, particularly early in life. A negative MRI is not a substitute for genetic testing for excluding the disease in asymptomatic kindreds. It is unclear at what age a brain MRI should be performed in asymptomatic children who carry a germline mutation, but this should certainly be performed when investigating any neurological symptoms.

Usually, when suggesting that the foci of susceptibility are likely small CMs, there are additional larger more classic appearing CMs, a positive family history, and/or a known genetic diagnosis to help support the diagnosis. It is, of course, conceivable that patients with CMs could also develop other non–CM-related hemorrhages related to hypertension, amyloid angiopathy, trauma, or other cause of hemorrhage. On follow-up imaging studies, it is important to focus on any change since prior imaging, including new CMs, change in size of a CM, change in blood signal characteristics, and development of edema in the surrounding parenchyma. It is possible to have changes on imaging that are asymptomatic, and it is important to note that not all changes on MRI constitute a significant symptomatic hemorrhage event. As with all neuroimaging, it is important to evaluate for findings of intracranial mass effect/herniation, hydrocephalus, other potential causes of the patient's symptoms, and any potentially important incidental findings.

MRI Acquisition

The MRI examinations for the evaluation of CMs should include standard MRI sequences including T1-weighted and T2-weighted sequences, T2 fluid-attenuated inversion recovery which can be useful for the identification of edema, and SWI (Siemens, Inc.), or similar susceptibility-sensitive gradient-based sequence such as SWAN (GE, Inc.), or VenoBOLD (Phillips, Inc.), and other routinely performed important sequences such as diffusion-weighted imaging (Table 2). Noncontrast enhanced T1-weighted images are key for the detection of T1 hyperintense blood products (methemoglobin). Performing SWI or a similar susceptibility-sensitive sequence is key for the identification of small CMs and will be more sensitive to the detection of small CMs than traditional T2* gradient recalled echo or traditional T2-weighted sequences.[1]

Gadolinium contrast-enhanced sequences may have a role in the identification of DVAs, although those can often also be identified on the susceptibility-sensitive sequences, identification of blood vessels to be considered for surgical planning/navigation, and in the evaluation of potential tumors, but would generally not be needed for follow-up of a known CM. As they are vascular structures, CMs and capillary telangiectasias can show enhancement, and the presence of enhancement should not be interpreted to mean there is a tumor, although prominent contrast enhancement can suggest hemorrhagic tumor (melanoma, pleiomorphic xanthoastrocytoma, etc.). When reporting MRI features of CM, it is recommended to note solitary vs multifocal CMs, the presence of subtle or more overt DVA, provide a count of larger CMs seen on T1/T2 conventional sequences and smaller lesions on susceptibility sequences, and provide a differential diagnosis (Table 3). Counting smaller CMs can be challenging, and it is preferable to avoid using terms such as "innumerable," which evoke needless patient anxiety, but rather report a range (ie, greater than 100 CMs) or estimate of burden (mild, moderate, or severe) when unsure about a specific high number of lesions.

TABLE 2. Recommended MRI Sequences for the Initial Diagnosis of CM

1. T1-weighted sequence without intravenous contrast
2. T2-weighted sequence
3. Susceptibility Sensitive Sequence (SWI, VenBold, SWAN or similar in brain, 3-dimensional MEDIC or similar in spine)
4. Other standard sequences (DWI, T2 fluid-attenuated inversion-recovery in the brain) to identify edema, infarction, or other CM mimics
5. Contrast enhanced imaging (T1 with Gadolinium) could be useful if need to evaluate for tumor rather than CCM and better delineate associated developmental venous anomalies
6. At least 1.5 T MRI is recommended, 3 T or stronger may be expected to see more small lesions

CM, cavernous malformation; DWI, diffusion-weighted imaging; MEDIC, Multi-Echo Data Image Combination; SWI, susceptibility-weighted imaging.

TABLE 3. Recommendations Regarding Imaging

Recommendation	Level of evidence
1. Brain MRI is the only imaging modality that is strongly recommended for the diagnosis and clinical follow-up of suspected or known CM.	Class 1, Level B-NR
2. Brain MRI for CM should include susceptibility-weighted sequences to establish whether there is one, or many, CM.	Class 1, Level B-NR
3. Catheter angiography is not generally recommended in the evaluation of CM, unless a differential diagnosis of arteriovenous malformation is being considered.	Class 3, Level C-EO
4. Follow-up imaging in CM should be considered to guide treatment decisions or to investigate new symptoms. Brain imaging should be performed as soon as possible after the onset of clinical symptoms suspicious of hemorrhage. CT may be appropriate in emergent situations to evaluate for detectable new hemorrhage and mass effect, but MRI is preferred and should be used as follow-up or as the definitive test (ideally within 2 weeks of symptom onset). Repeat MRI should be performed in conjunction with new or worsened symptoms to detect any new CM lesion, interval growth, or new ICH.	Class I, Level B-NR
5. In patients with prior cranial irradiation, an MRI of the brain is indicated for new onset severe headache, seizure, and focal neurological deficit due to the potential for CM development.	Class I, Level C-LD

CM, cavernous malformation; CT, computed tomography; EO, expert opinion; ICH, intracranial hemorrhage; LD, limited data; NR, nonrandomized.

Automated techniques are being developed to assist in such CM counts.[64]

A spinal CM should be included for patients with neck or back pain, limb pain, numbness, or weakness unexplained by brain lesions. For suspected spinal CMs, a susceptibility-sensitive sequence such as 3-dimensional Multi-Echo Data Image Combination (Siemens) should be used in addition to standard T1-weighted and T2-weighted MRI sequences as this can help show small CMs similar to what SWI does in the brain.[65,66] Although FCM cases often harbor spinal CMs, it is unclear if the diagnosis of occult lesions in asymptomatic cases will alter clinical management.[66,67]

Follow-Up MRI

Optimal intervals for routine follow-up imaging are not well established. It is known that patients with FCM form new CMs over time and some new CM development and change over time can be expected depending on the time interval. Changes in symptoms or new symptoms do warrant repeat imaging, which would ideally be by MRI. However, depending on symptom severity, presentation, and emergent availability of MRI, these may warrant CT to evaluate for large hemorrhage and mass effect prior to MRI availability. Routine scheduled follow-up MRI may be useful to document the stability of CMs which have previously bled or enlarged or in other situations per the clinical judgment and shared decision making of the neurological or neurosurgical provider and patient. There is recent evidence that subclinical changes on surveillance MRIs may herald subsequent symptomatic hemorrhages,[32] while the impact on clinical decisions remains controversial.[68]

Advanced imaging techniques beyond standard MRI sequences and a table summarizing reporting considerations are presented in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

DIAGNOSTIC CRITERIA

Based on the preceding genetics and imaging sections, we propose recommended diagnostic criteria for CM, all of which are based on limited classes and levels of evidence (Class 2a; Level C-LD).

1. Typical "popcorn" like appearance of CM with surrounding "hemosiderin ring" on T2 MRI establishes a diagnosis of CM. The presence of an associated DVA or multifocal CM further confirms the diagnosis of sporadic/solitary or multifocal/familial disease, respectively.
2. Multiple clustered CMs in association with a single DVA can be considered as solitary (clustered) CM and sporadic disease.
3. The presence of a growing CM and/or dense contrast enhancement raises a differential diagnosis of tumor, which can be adjudicated by histopathological biopsy on CM excision.
4. Contrast enhancement in CM lesions and capillary telangiectasias should not, by itself, imply tumor.
5. Tiny hemorrhagic lesions without any associated typical CM lesions (ie, "popcorn" like with "hemosiderin ring") may be cerebral microbleeds rather than CM. These are more common in association with aging and vascular risk factors and typically without family history. Genetic testing with evidence of mutation in a CM gene can help resolve the differential diagnosis.
6. Family history of multiple affected relatives raises a question of FCM disease, warranting genetic testing for confirmation. Multifocal CMs without an associated DVA also raise the possibility of FCM, which genetic testing can confirm.
7. Absence of CM on brain MRI does not exclude carrying the mutation in cases with FCM. Patients who carry a familial

pathogenetic CM mutation may develop CMs in the future and can pass the genetic mutation to their children.

SURGICAL CONSIDERATIONS

Asymptomatic CMs and Associated Venous Anomalies

The benign progression of incidental CMs, characterized by a minimal hemorrhage risk, generally precludes the necessity for prophylactic surgery in asymptomatic patients.[1] Subclinical changes in CMs may herald future bleeding and influence the decision to resect a solitary sporadic CM.[32] Surgical resection of CMs can decrease future hemorrhagic episodes and improve seizure control in affected individuals.[69] Yet, variable morbidity associated with this intervention necessitates a prudent assessment of surgical indications.

There have been no new data regarding resection of associated DVA, with some surgeons advocating avoiding DVA dissection to prevent complications such as edema, hemorrhage, and/or venous infarcts, although this practice remains in evolution. Although recent evidence has confirmed somatic mutations in the DVA contribute to CM pathogenesis,[58] there are no controlled data regarding the greater or lesser likelihood of CM recurrence with or without DVA resection.

CM Multiplicity and Location

Most surgical reports continue to focus on individual CM lesion location and symptomatic status,[70] and there has been no evidence of different surgical outcomes for resection of solitary vs multifocal/familial CMs, nor those specifically associated with DVA. Surgical resection is more likely to be considered curative in solitary CMs, and these are more likely to be considered for resection with subtle symptoms or asymptomatic CM growth or bleed.[32]

In patients with lobar CM in noneloquent areas, surgery may be considered after a first symptomatic bleed as the risk of permanent complications is relatively low.[71] Similarly, patients with symptomatic CMs in eloquent areas such as the primary sensorymotor cortex, dominant hemisphere speech areas, and primary visual cortex should be offered surgical resection after the first symptomatic bleed if the CM is easily accessible and can be removed with an acceptably low risk.[1,71]

Follow-up studies have suggested that the transition from independent to dependent status (mRS score ≤ 2 to ≥ 2) usually occurs after a second symptomatic bleed in deep-seated and brainstem CMs.[1] Hence, conservative management after a first symptomatic bleed and consideration for surgery only after a second bleed is a reasonable alternative management strategy in brainstem CMs. Grading systems proposed to guide surgical decisions in brainstem CMs are considered in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

CM Associated with Seizures

In a patient who presents with a first-time seizure from a CM without associated hemorrhage, a conservative approach with antiseizure medications (ASM) is recommended.[1] Surgery should be considered after a first seizure in patients with a desire to stop ASMs and in those who are intolerant to ASMs.[1] Surgery consisting of pure lesionectomy with (when possible) excision of the hemosiderin-stained brain has an 88% chance of achieving sustained (at least 2 consecutive years of International League Against Epilepsy Class 1 at follow-up) seizure-free outcome vs 32% in patients treated with initial medical management alone (Class 3 evidence).[44]

Patients with persistent seizures despite ASMs should undergo specialized evaluation in a center that specializes in seizure disorders. Because of the additional protective effect of surgery against future hemorrhage, surgery should be considered although patients may not strictly fulfill the criteria for drug-resistant epilepsy.[1] Specific surgical strategies are further discussed in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

Surgical Considerations for Pediatric Intracranial CM

Pediatric patients with CM have distinct factors that may influence surgical decision making, particularly their expected longer lifespan relative to adults and the relative plasticity of the developing brain that affords more resilience to surgery than adults. Overall, surgery is a reasonable first-line therapy for symptomatic, growing, or bleeding CMs that are in noneloquent locations.[72,73] The current evidence suggests that operating in higher-risk locations, such as the basal ganglia, thalamus, cerebellum, brainstem, and spine, may benefit from individualized assessment of patient-specific anatomy with greater risk for operative-related neurological deficits in brainstem CMs.[74-78] Specific considerations related to pediatric epilepsy surgery are presented in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

Surgical Considerations for Older People with Intracranial CM

Older people with CM have distinct factors that may influence decision making around surgical intervention, particularly including the consideration of medical comorbidities that may affect the risk of potential interventions, in addition to the recognition that QoL has particular importance for many older patients. Overall, surgery for symptomatic, growing, or bleeding CMs that are in noneloquent locations may be considered, in the context of the risk profile for people in this population. Operative risks are greater, and worse outcomes are more likely, especially in patients older than 60 years and for CMs located within the brainstem.[79,80] Other surgical considerations in older patients are presented in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

Surgical Considerations for Spinal Cord CM

The risk and morbidity of surgical resection varies according to the location (especially axial) of the spinal CM, baseline neurological function, and surgeon/institutional experience.[3,4,10,14,15,21,22,24] Additional risk/benefit context is provided by patient comorbidities and preferences. The outcome of brainstem lesion resection can be correlated with preoperative grading schemes, which have been

validated.[81,82] In most studies, patients who opt for surgery have greater neural impairment, a shorter symptomatic time course, and a more dorsal or dorsolateral location compared with patients managed conservatively.[1,2,14,15,24] This type of selection bias makes it difficult to directly compare surgical to nonsurgical treatment (ie, natural history) in many comparative studies. Many acute hemorrhagic events often show spontaneous recovery of varying degrees over time.[4,19] It can be difficult to accurately allocate natural history neurological improvement vs surgical intervention functional restoration, especially when surgery is performed soon after a disabling hemorrhage.

Classifications of spinal CMs, surgical approach, technique, and outcome are expanded in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

Minimally Invasive Operative Approaches for CM

Laser Ablation, Minimal Access Neuro-Port, and Endoscopic

As an alternative to open microsurgical resection of CMs, minimally invasive surgical approaches have been proposed to reduce adverse surgical complications from CM excision, in particular, CMs located in deep or eloquent territories, and as an alternative strategy for drug-resistant epilepsy cases. There is growing use of laser interstitial thermal ablation (LITT) approaches for drug-resistant epilepsy cases with a low reported hemorrhage rate 3.1% and seizure-free Engel class 1 outcomes of 78%-83% comparable with the gold standard open microsurgery approaches.[83,84] However, in a large meta-analysis of individual patient data, CMs treated with LITT ablation that went on to have recurrent seizures were all subsequently treated with microsurgical resection.[84,85]

LITT has been used for CM treatment in nearly all supratentorial and infratentorial locations with proposition for deep or eloquent locations as an alternative for cases deemed nonoperable. Selection bias in these compiled, mainly single-center series may favor the treatment of CMs appearing in safer brainstem locations and without hemorrhagic features. In addition, LITT precludes the use of intraoperative electrocorticography, a combinatorial operative strategy effective in epilepsy surgery cases.[84] Other considerations regarding minimally invasive surgery are presented in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

Stereotactic Radiosurgery

Stereotactic radiosurgery (SRS) has been proposed as an alternative treatment for symptomatic CM in eloquent areas.[1] A recent meta-analysis comparing the risks and benefits of microsurgery, radiosurgery, and observation found that microsurgery has a 1% to 2% risk of perioperative fatality, 3% postoperative hemorrhage rate, and cumulative long-term morbidity of 11%. Radiosurgery, by comparison, had a 1% risk of periprocedural death, a 14% hemorrhage rate, and a 10% risk of long-term morbidity.[86] Given that the surgical efficacy was 97% compared with 86% for radiosurgery for roughly the same morbidity and mortality, microsurgical resection was considered the optimal first-line therapy.

No comparison with LITT exists, but as experience grows with the latter, a direct comparison may prove illustrative.[87] Another meta-analysis demonstrated that the efficacy of SRS was enhanced when SRS is chosen early after bleeding rather than delayed, and it also supported a higher marginal dose (>16 Gy) for better bleeding control, with results being best for nonbrain stem CCMs of <3 cm^3 that lacked a coexisting DVA.[88] A single-center study suggests that CCMs <1 cm^3 may fare even better,[89] and another meta-analysis confirmed that the effect on rebleeding was most pronounced in the first 2 years after the incident hemorrhage.[90]

Short-term follow-up of patients undergoing treatment less than 5 years before failed to demonstrate large differences in quality-adjusted life years despite disparate bleed rates.[69] A small single-center series of pediatric patients only suggested that lower marginal doses of 12 GY may be sufficient to reduce bleeding and improve seizures and may decrease treatment-associated edema,[91] and lower doses may be sufficient if the goal is merely to enhance seizure control.[92] There also remains concern over whether radiation exposure may enhance the genesis of new CMs in familial cases.[1]

Supplemental Digital Content 1 (http://links.lww.com/NEU/E735) presents further considerations regarding the lack of high-quality evidence and the need for future research regarding surgical indications.

Postoperative Imaging Follow-Up for CM

Patients treated with surgical resection are commonly followed with postoperative MRI studies to confirm durable response to therapy and to monitor for recurrence, hemorrhage, or growth of residual CMs. Immediate postoperative MRI (within 72 hours) has a positive predictive value of 67% and a negative predictive value of 97% in confirming complete resection.[93] Long-term residual/recurrence rates vary from 11% to 23% overall, with higher rates reported in pediatric patients and delayed postoperative hemorrhage found on follow-up in 5.6% of all operative cases and 29% of all known residual/recurrent CMs, subject to average follow-ups of 5.6 to 6.7 years.[73,94] Of all identified recurrent/residual CMs, 58% underwent reoperation.[94] Overall, the combination of relatively high rates of recurrence/regrowth—especially in pediatric patients, subtotally resected CMs and brainstem CMs—coupled with actionable outcomes in a large proportion of identified recurrences/residual growth, support as reasonable the practice of routine follow-up for a period of about 5 years, with pediatric guidelines specifically suggesting annual MRIs.[72] A comprehensive summary of neurosurgical recommendations is presented in Table 4.

NEUROLOGICAL CONSIDERATIONS

Management of Symptoms

Seizures

Seizures are the most common symptom associated with CM.[95] It is important for a neurologist to assess a patient's symptoms and perform an electroencephalogram when there is uncertainty about whether symptoms are truly seizures, when it is

not clear if the seizure is related to the CM present, or to determine which CM is causing seizures in the case of multiple CM. In some situations, prolonged electroencephalogram monitoring (ambulatory or epilepsy monitoring unit) may be useful.

CM-related epilepsy (CRE) is more common in patients with a supratentorial, cortical CM, especially when present in the temporal lobe.[96,97] The risk of CRE may be associated with the volume of displaced gray matter by the CM.[98] In definite CRE, the risk of recurrent seizure after a first unprovoked seizure is high (>90% at 5 years).[43,99] Therefore, in clinical practice, it is common to start with ASM. Decisions about which ASM to start depend on patient-specific factors and should be individualized.[100] Approximately 50% to 60% of patients will become seizure-free on medication after the first diagnosis of CRE.[43,95,101,102] Drug-resistant epilepsy, defined as a failure due to lack of efficacy of 2 appropriately chosen and dosed ASMs[103] may develop in approximately 20% to 25% of patients and is more commonly associated with temporal CM location.[104,105]

In addition to treating the seizure, patients with a seizure disorder should avoid medications and activities that may could increase the risk of seizure and potential for personal injury or suffering. Patients should also follow the individual state law or other governing jurisdiction about seizures and driving. Interactions of seizure medications with other medications, birth control, and effects on pregnancy and vitamin D should be considered as applicable.

Headache

The incidence of headache in the CM population is common, with reporting as high as 52%.[106] In some cases, the relationship of the headache to the CM may be difficult to determine. There is general agreement in the field that headaches in patients with a hemorrhagic CM near the pial surface or in the presence of associated hydrocephalus are related. However, a hemorrhagic or nonhemorrhagic CM fully within the brain parenchyma is theoretically less likely to cause headaches since it is deep to the pain-sensitive dura. The International Classification of Headaches ICHD-3 has put forth criteria for headache attributed to CM (Table 5). If a patient does not meet these criteria, appropriate ICHD-3 criteria should be considered.

In patients meeting criteria for migraine who happen to have a nonhemorrhagic CM, standard migraine therapy is generally recommended. One case report of a patient with CM experiencing hemorrhage after onabotulinumtoxinA injection for migraine headache was published.[107] The doses of onabotulinumtoxinA toxin exceeded standard doses for migraine. In a study of 329 patients with either spinal or cerebral CM, the use of nonaspirin nonsteroidal anti-inflammatory drugs, triptans, and onabotulinumtoxinA did not increase the risk of hemorrhage. In this study, doses of onabotulinumtoxinA were all less than 200 units. The study was limited in that the duration of use was not assessed.[108] There are no safety data on calcitonin gene-related peptide inhibitor use in patients with CM.

Focal Neurological Deficit

Patients with CM may experience a variety of neurological deficits including acute, subacute, and chronic deficits. Typically these deficits occur in the setting of cerebral hemorrhage or lesion growth. Unless these deficits resolve quickly, patients are referred for rehabilitation. Little is known or referenced in the literature about any precautions or benefit of rehabilitation. However, based on extrapolation of benefit of therapy in hemorrhagic stroke and related conditions, the authors support rehabilitation efforts to help improve QoL factors including a return to independence, weight bearing, and improved emotional health.

In select situations, facial reanimation surgery and strabismus surgery are considered for those with persistent deficits from brainstem CM hemorrhage and/or surgery once clinical improvement plateaus.

Medical Management of CM in Children

Twenty-five percent of sporadic and familial CMs occur in pediatric age groups, and based on a series of 105 consecutive probands, up to 20% of index cases in FCM are in children younger than 10 years and 33% younger than 18 years.[109] Similar to adults, children may present with incidental or symptomatic CM including seizures, headaches, and acute neurological events. High rates of incidental CM discovery may be seen in pediatric practice in children and adolescents imaged for presenting complaints of headache, traumatic brain injury, developmental delay, or new onset seizure.

Survivors of childhood cancers are a growing population at risk for treatment-acquired CM.[110] After cranial irradiation, these patients manifest progressive large and small vessel intracranial arterial disease, chronic encephalopathy, and independent risks for early cognitive decline.[111] This risk is compounded by the additional radiation dosing suffered in repeated CT and dental X-rays required for disease management. Controversy exists on how best to monitor and respond to radiation-induced CM in pediatric cancer survivors. Using a Delphi process, 45 experts in childhood cancer survivorship demonstrated less than 70% agreement on whether to refer newly identified CM to neurology and/or neurosurgery, 70% to 89% agreement on repeat imaging timing (1-2 years), and whether to screen for additional stroke risk factors (lipid panel, HbA1C, and serum glucose), and high-level agreement not to use antiplatelet therapy.[111] In addition to developing optimal disease surveillance practices, more data will emerge in the coming decades as the long-term effects of proton beam treatment manifest.

Optimal surveillance schemes are of interest to all pediatric patients known or at risk for CM development. Additional risks are most readily identified in younger and intellectually delayed children who require anesthesia for safe and accurate MRI acquisition. Clinicians of children with solitary CM must determine whether the CM is sporadic or familial. To make this determination, the clinician uses a detailed history and thorough brain imaging that includes gradient recalled echo or SWI to look for

TABLE 4. Recommendations Regarding Surgical Management of CMs[a]

Recommendation	Level of evidence
Recommendations regarding surgery for intracranial CM	
1. Surgical resection should not be performed for asymptomatic, stable CM if located in eloquent, deep or brainstem areas, nor in cases with multiple asymptomatic CMs.	Class 3, level C-LD
2. Surgical resection may be considered in solitary asymptomatic CM if easily accessible in noneloquent area, to prevent future hemorrhage, because of psychological burden, expensive and time-consuming follow-ups, or per lifestyle or career considerations.	Class 2b, level C-LD
3. Surgical resection of asymptomatic CMs for the specific goal of safer pregnancy is not recommended.	Class 3, level C-LD
4. Early surgical resection of CM for seizure control can be useful, especially with medically refractory epilepsy, if the epileptogenic CM responsible for epilepsy is identified. CM excision is reasonable, rather than radiosurgery for epileptogenic CM.	Class 2a, Level B-NR
5. Surgery may be considered in symptomatic easily accessible CM lesions, with mortality and morbidity equivalent to living with the CM for about 2 y.	Class 2b, Level B-NR
6. Surgical resection may be considered in deep CM lesions if symptomatic or after prior hemorrhage, with mortality and morbidity equivalent to living with the lesion for 5-10 y.	Class 2b, Level B-NR
7. After reviewing the high risks of early postoperative mortality and morbidity and impact on quality of life, it may be reasonable to offer complete surgical resection of brainstem CM after a second symptomatic bleed as brainstem CMs have a higher risk of rebleeding.	Class 2b, Level C-LD
8. Resection of brainstem CM after a single disabling bleed may be considered.	Class 2b, level C-LD
Radiosurgery and minimally invasive approaches for intracranial CM	
9. Radiosurgery may be considered for solitary CM lesions with previous symptomatic hemorrhage if the CM lies in eloquent areas that carry an unacceptably high surgical risk.	Class 2b, Level B-NR
10. Radiosurgery is not recommended for asymptomatic CMs, nor in familial CMs with concern about de novo CM genesis.	Class 3, Level C-LD
11. Laser thermal ablation of CM is reasonable to consider for smaller symptomatic CM and those causing seizures, with weaker evidence of safety in larger CM or those with recent hemorrhage.	Class 2b, Level B-LD
Surgical treatment of pediatric and older patients with CM	
12. Surgery can be beneficial for pediatric CM, with stronger indications, including symptomatic presentation or CM-related epilepsy, and with the same consideration regarding the inclusion of risk assessment relative to location.	Class 2a, Level B-NR
13. Surgery can be beneficial for geriatric CM, but indications may be more limited given increased surgical risk with older age. Stronger indications include symptomatic presentation or CCM-related epilepsy in the absence of medical contraindications	Class 2b, Level C-LD
Surgical treatment of spinal CM	
14. Surgical resection may be considered for dorsal or dorsolateral spinal CMs with exophytic or pial presentation.	Class 2b, level C-EO
15. Surgical resection may be considered for dorsal or dorsolateral hemorrhagic spinal CMs with exophytic or pial presentation in patients with minimal or transient symptoms but without functional impairment.	Class 2b, level B-NR
16. Surgical resection may be considered for dorsal or dorsolateral surface or exophytic spinal CMs in patients with single acute neurological impairing event.	Class 2b, level B-NR
17. Surgical resection may be considered for patients with single acute neurological impairing event for an imbedded (completely intramedullary) spinal CM.	Class 2b, level C-EO
18. Surgical resection may be considered for patients with >1 acute neurological impairing hemorrhagic events for an imbedded or ventral spinal CM.	Class 2b, level C-EO
19. Surgical resection may be considered for patients with progressive neurological deterioration with dorsal or dorsolateral spinal CMs.	Class 2b, level B-NR
20. Surgical resection may be considered for patients with progressive neurological deterioration with imbedded (intramedullary without surface presentation) or ventrally located spinal CM.	Class 2b, level C-EO

TABLE 4. Continued.

Recommendation	Level of evidence
21. Urgent surgical resection may be considered with an acute spinal CM hemorrhage with rapid neurological deterioration subject to patient comorbidities and preferences.	Class 2b, level C-EO
Postsurgical imaging follow-up of CM	
22. Early postoperative MRI may be considered to assist with confirming gross total resection (Class 2b, Level C-LD). Ongoing surveillance following resection is reasonable, with suggested annual MRI scans for at least 5 y, particularly in pediatric cases.	Class 2a, Level C-LD

CM, cavernous malformation, EO, expert opinion; LD, limited data; NR, nonrandomized.
[a]**Supplementary Materials** present further considerations regarding the lack of high-quality evidence and the need for future research regarding surgical indications.

additional small dot-like CMs and/or developmental venous anomalies.

For children at risk for FCM, optimal timing for diagnosis confirmation and disclosure of results is an ethically complicated process. Disclosure of a disease-confirming result may not be developmentally appropriate for some youths who may be asymptomatic or otherwise unable to appropriately intellectualize the information. Discussion of autosomal dominant inheritance patterns, variable penetrance, and family planning counseling is often of major concern to parents but may be ahead of the developmental capacity of the child. Although there are clear benefits of early diagnosis to facilitate surveillance and management at earlier stages of disease, natural history studies suggest that symptomatic presentation is often delayed until adulthood, except for *CCM3* patients. The child's autonomy should be discussed with the parent(s) in a shared decision-making process under the guidance of a licensed genetic counselor.

Childhood cerebrovascular medicine continues to develop an independent evidence basis for ischemic and hemorrhagic stroke management in the young. Recent key advances are the incorporation of the International Pediatric Stroke Organization (https://internationalpediatricstroke.org)—bringing together multispecialty expertise for advocacy and clinical trial development—and the publication of a comprehensive scientific statement endorsed by the American Heart Association/American Stroke Association.[72] According to data aggregated in the scientific statement, approximately 75% of ICH in childhood is related to an underlying vascular lesion of which CM is a minority of cases. Specific guidance on diagnostic confirmation, genetic testing, treatment selection, and need for further study are outlined therein and concordant with the present guideline.

Management of CM During Pregnancy

In the 1980s and early 1990s, a small number of studies suggested that pregnancy contributed to a potential aggressive clinical course. Recently, however, the data from several large series suggest that pregnancy does not increase the risk of clinical symptoms and hemorrhage rate compared with nonpregnant CM patients,[28,112,113] although some controversy remains.[114] In a review of 349 pregnancies with 49 hemorrhages during childbearing years, Witiw et al[112] found only 3 hemorrhages occurred during pregnancy. The study compared the number of clinically significant hemorrhages divided by the time in the pregnant state vs the number of hemorrhages during the nonpregnant state

TABLE 5. Headache Classification in Relation to Cavernous Malformation

International classification of headaches: headache attributed to cavernous angioma
A. Any new headache fulfilling criterion C
B. A CM has been diagnosed
C. Evidence of causation demonstrated by at least two of the following:
1. Headache developed in close temporal relationship to other symptoms and/or clinical signs of CM or led to its discovery
2. Either or both of the following: (a) Headache has significantly worsened in parallel with other symptoms or clinical or radiological signs of growth of the CM and (b) headache has significantly improved after resection of the CM
3. Headache is localized to the site of the CM
D. Not better accounted for by another ICHD3 diagnosis

CM, cavernous malformation, ICHD, International Classification of Headaches Disorder.
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TABLE 6. Recommendations Regarding Neurological Management

Recommendation	Level of evidence
1. Antiseizure medication for first seizure thought to be due to a CM is recommended.	Class I, Level B-NR
2. When considering surgery in patients with seizure and nonhemorrhagic CM, especially those with familial form, a careful review by a neurologist and electroencephalogram should be considered to assure that the relationship of the CM to the seizure and that the appropriate CM is being considered for resection or ablation when multiple CMs are present.	Class I, Level C-EO
3. In patients with CM presenting with headache and no secondary cause, the primary headache disorder should be classified and treated according to standard headache practice.	Class I, Level C-EO
4. The use of nonaspirin NSAIDs can be used with caution in patients with CM and nonhemorrhagic lesions.	Class 2b, Level C-LD
5. Shared decision making between parents and a genetic counselor is recommended before considering disclosure of CM diagnosis to a child.	Class I, Level C-EO
6. Patients with known familial or multifocal CM should consider genetic counseling before pregnancy.	Class I, Level C-EO
7. Folate supplementation should be considered in patients with CM and seizure disorder on antiseizure medication who desire pregnancy.	Class I, Level A[a]
8. Patients may be counseled that the risk of neurological symptoms during pregnancy with CM is likely not different than the nonpregnant state.	Class 2a, Level B-NR
9. MR imaging without contrast should be considered in patients with CM that develop new neurological symptoms during pregnancy or while lactating.	Class 2a, Level C-EO
10. The prospective risk of CM hemorrhage in patients necessitating antithrombotics is low and the presence of CM should not preclude their use if deemed necessary.	Class 2a, Level B-NR
11. For patients presenting with acute ischemic stroke who are known to harbor an unruptured and untreated CM, the risk of administration of thrombolysis is not well established. Because of the increased risk of ICH in this population of patients, IV alteplase may be considered if indicated for acute ischemic stroke.	Class 2B, Level C-LD
12. Sex hormones (including exogenous oral estrogen and progesterone) may increase risk of CM hemorrhage and caution regarding their use is recommended.	Class 3, Level C-LD
13. The long-term efficacy of statins for reducing CM hemorrhage risk or preventing new CM development is not known. A statin can be considered in patients with CM and elevated cholesterol according to standard medical use guidelines	Class 1, Level C-EO
14. Propranolol is safe and tolerable at low doses in patients with familial CM. The long-term efficacy of propranolol for reducing CM hemorrhage or preventing new CM formation in familial CM is not clear.	Class2b, Level B-R
15. Vitamin D supplementation should be considered in CM patients with vitamin D deficiency for bone health; the effects on CM hemorrhage are less clear.	Class 1, Level A[a]
16. Vitamin D supplementation is reasonable in CM patients with unknown 25-OH-vit D levels, especially those on antiseizure medications or with risk for vitamin D deficiency.	Class 2b, Level B-NR
17. Aerobic activity is reasonable for patients with CM.	Class 1, Level C-LD
18. Binge alcohol drinking should be avoided in patients with CM.	Class 1, Level C-LD
19. A diet low in processed foods or emulsifiers may be considered to reduce gut leakiness which has implications for CM development.	Class 2a, Level C-EO
20. There are limited data suggesting blood pressure is a risk factor for CM hemorrhage. Assessment and treatment to control high blood pressure is recommended according to standard guidelines.	Class I, Level A[a]
21. An assessment for anxiety and referral to appropriate resources is recommended in patients with CM.	Class 2a, Level C-EO

25-OH-vit D, 25-hydroxy vitamin D; CM, cavernous malformation, EO, expert opinion; LD, limited data; MR, magnetic resonance; NR, nonrandomized; NSAID, nonsteroidal anti-inflammatory drug.
[a]Level and class of evidence derived from non-CM trials.

between the ages of 15 and 44 years. The hemorrhage rate for pregnant women was 1.15% per person-year compared with 1.01% per person-year for nonpregnant women. The authors concluded that hemorrhage rate did not differ dependent on pregnancy. This conclusion assumes that the CM was present between the ages of 15 and 44 years. Similarly, Kalani et al[28] found a low hemorrhage rate in 64 patients with CM (28 sporadic; 36 familial) who had 168 pregnancies. This study agreed that there is no increased risk during pregnancy. This study was limited in that confirmation of clinical events radiologically was not always possible. The Kalani and Witiw studies are limited by the time of diagnosis of the CM relative to the pregnancy. Given many patients are diagnosed with CM after childbearing years, Joseph et al[113] looked at patients with pregnancy after CM diagnosis. In this study, no symptomatic hemorrhages occurred in 32 patients with pregnancy after the diagnosis of CM was made. This study was limited by the small number of patients with pregnancies after CM diagnosis.

Special considerations should be made when counseling a patient with CM who is planning pregnancy or is pregnant. For those with multiple CMs, genetic counseling may be discussed. With those patients who suffer a seizure disorder due to CM, to ensure health of the newborn child, discussion of the appropriate ASM to reduce teratogenic side effects and folate supplementation should occur before the patient becomes pregnant, when possible. ASM levels may need to be closely monitored. If focal neurological deficits, an acute, severe headache, or a flare-up in seizures occur during pregnancy, an MRI scan without contrast can be considered. If a patient has a brain hemorrhage during pregnancy, the severity of symptoms and risk of recurrent hemorrhage need to be weighed against the risk of surgical intervention at that point in the pregnancy. It is generally agreed that vaginal delivery is appropriate in most patients unless there is a neurological deficit that precludes such or recent hemorrhage.

Medication Usage for Comorbid Conditions in Patients with CM

Patients with an existing CM may have comorbid conditions that require medications that could have a negative effect on hemorrhage risk. Concerns have arisen regarding the use of antithrombotics (antiplatelet agents or anticoagulants) and thrombolytics in addition to those medications with effects on coagulation (eg, fish oil, vitamin E supplementation, selective serotonin reuptake inhibitors, and nonsteroidal anti-inflammatory drugs) because of the leakiness of the endothelium. However, owing to intracavernous clotting with resultant poor venous outflow also theoretically leading to CM hemorrhage, medications with thrombotic risk (eg, female hormones, fertility medications) have also raised concern.

Antithrombotics

A meta-analysis by Zuurbier et al[115] assessing 1342 patients with CM, 253 of whom were taking antithrombotics, showed a lower risk of CM hemorrhage in those patients taking antithrombotics (3%) vs those not on antithrombotics (14%) over an average of 7.4 years, even after adjusting for age, history of CM hemorrhage, and brainstem location. The duration of exposure and dose of medications were not known, which may limit the interpretation of the data. Multiple other nonrandomized cohort studies have yielded similar results, and data held true whether familial or sporadic forms were assessed.[84,115,116] Notably, most patients in these studies were taking aspirin rather than anticoagulants, raising the question of whether the potential protective effect is related to its antithrombotic vs anti-inflammatory properties. Supporting the antithrombotic theory is data from Previch et al[116] demonstrating that other medications and supplements with potential antithrombotic qualities (fish oil and serotonin reuptake inhibitors) similarly reduce the risk of CM bleeding. There are no clinical trial data related to aspirin or anticoagulants at this time. There are limited data on direct oral anticoagulants.

Thrombolytics

Data supporting the safety of thrombolytic use for cerebral ischemia in patients with a concomitant CM are limited and inconclusive. Erdur et al[117] report no significant difference in symptomatic ICH and parenchymal hemorrhage rate when comparing 9 patients with CM compared with 341 patients without CM undergoing thrombolysis for probable cerebral ischemia. One patient with CM had a symptomatic ICH at the site of the cerebral infarction, distant to the CM. Another patient with a CM with associated subacute hemorrhage had evidence of expansion of the hemorrhage with symptoms. In the latter patient, the original symptoms of aphasia were felt to be due to a seizure rather than cerebral ischemia. Schwarzbach et al[118] further present 13 patients with CM and thrombolytic use and found no significantly increased risk of hemorrhage compared with controls. The American Stroke Association guidelines recommend: For patients presenting with acute ischemic stroke who are known to harbor an unruptured and untreated intracranial vascular malformation, the usefulness and risks of administration of thrombolytics are not well established. Because of the increased risk of ICH in this population of patients, IV thrombolytics may be considered in patients with stroke with severe neurological deficits and a high likelihood of morbidity and mortality to outweigh the anticipated risk of ICH (COR IIB; LOE C-LD).[119]

Female Hormones

Some believe that intracavernous thrombosis leads to poor venous outflow and subsequent extralesional bleeding, akin to cerebral venous thrombosis. Estrogen is known to increase thrombosis. Thus, estrogen could theoretically increase risk of hemorrhage from CM. In addition, researchers have suggested progesterone may negatively influence the CM complex.[120] Estrogen use was noted to increase the likelihood of initial clinical presentation with CM hemorrhage in female patients with CM in 1 study.[121,122] Subsequently, a meta-analysis assessing use of female hormones in patients with CM compared the rates of

prospective hemorrhage after diagnosis in female patients.[123] The rate of CM hemorrhage was higher (33.6%) in those on female hormones than those without (15.6%) over an average follow-up of 3.3 years, even after adjusting for age, mode of presentation, and CM location. The odds of hemorrhage increased further when the patient was taking oral contraception and using tobacco. This exploratory study raises concerns over the use of female hormones in patients with CM but has limitations. The dose, duration of use, and mode (vaginal vs oral vs IUD) were not reported. The study did not include some female hormones (eg, progesterone only IUD). In addition, whether there is a third factor (eg, Factor V Leiden or tobacco use) that increases the risk in some patients but not others remains under investigation. There are limited data on fertility medications, but some may also increase thrombotic risk, and therefore, caution would be advised.

Potentially Beneficial Medications

In patients with deep-seated CM or familial CM, an alternative to surgery has been an important goal in CM research. Emerging data from basic and translational science suggest that select medications may stabilize CM or prevent further hemorrhage. The CM with symptomatic hemorrhage trial readiness project assessed clinical and radiographic features of trial-ready patients to facilitate these medications moving forward.[124]

Statins

Statins have been suggested in laboratory and preclinical studies as a potential therapy for CM by indirectly inhibiting rho kinase, a regulator of endothelial leakiness. Observational cohort studies have yielded mixed results, with some showing a protective effect of statin when combined with aspirin and some have shown a neutral effect on hemorrhage risk with statin use.[84,116,125,126] Cohort studies are limited by the lack of ability to control the dose, type of statin, or duration of exposure, which may be important to rho kinase inhibition.[127] A small pilot study of 10 patients with CM, randomized to either receive simvastatin 20 to 40 mg daily for 3 months or not, assessed effects on permeability as measured by dynamic contrast-enhanced perfusion MRI.[128] CM lesions showed increased permeability compared with white matter, but there was no difference in CM permeability between those receiving statin compared with those without. The Atorvastatin Cavernous Angioma Symptomatic Hemorrhage Exploratory Proof of Concept study has argued that a higher dose of a high-potency statin is necessary for sufficient rho kinase inhibition.[127] This study randomized CCM patients with symptomatic hemorrhage within 1 year to either 80 mg of atorvastatin or placebo and completed enrollment in 2023, with final results expected in 2025. Additional specific rho kinase inhibitors are expected to begin clinical trials soon.[129,130]

Beta Blockers

Propranolol, a nonselective beta blocker, is commonly used for infantile hemangiomas which share similar histopathological features with CM. Subsequently, a few case reports suggested that propranolol may reduce the size of CM.[131,132] Nonrandomized cohort studies have shown mixed results regarding beta-blockers with some suggesting a beneficial effect[126] and some with a neutral effect.[84,116,125,133] However, cohort studies are limited by dose, type of beta blocker, and duration of exposure. These factors may affect the efficacy.[134] Goldberg et al[133] further assessed the risk of presentation with hemorrhage or prospective hemorrhage by separating the types of beta-blockers (any vs beta-1 selective beta blockers vs unselective beta blockers). The researchers did not find any association with hemorrhage risk. The TREAT_CCM trial randomized patients with familial CM and symptoms 2:1 to either propranolol or placebo.[135] The propranolol dose started at 10 mg BID and was increased as tolerated to 160 mg BID. The primary outcome was a new symptomatic hemorrhage or focal neurological deficit attributed to the CM over 24 months. The phase 2 pilot study[135,136] consisting of 95 patients concluded that propranolol was safe, well-tolerated, and may be beneficial. The primary outcome was seen in 4.0% of the treated group vs 8.0% of the placebo group (hazard ratio 0.43; 80% CI 0.18-0.98.). Seizure rates, de novo CM rates, and serious adverse effects did not differ between groups. Absolute numbers remain small in this study, and most patients with symptomatic hemorrhage had nondisabling symptoms. Nonetheless, further study is necessary to see if this may be a viable long-term option for familial CM patients.

Cholecalciferol

In vivo studies demonstrated improved endothelial integrity in *CCM2* deficient cell cultures when treated with cholecalciferol (vitamin D3) likely through antioxidant and anti-inflammatory properties.[1] The role for vitamin D in CM is further supported by data demonstrating CM disease severity is affected by polymorphisms in vitamin D metabolism genes.[137] Subsequently, 2 cohort studies assessing 25-hydroxy vitamin D (25-OH Vit D) levels in patients with CM demonstrated more aggressive behavior in patients with low 25-OH Vit D levels.[121,138] Girard et al[138] demonstrated an inverse relationship between 25-OH Vit D levels and aggressive behavior defined as young onset, 2 or more symptomatic bleeds, or high CM burden. Flemming et al[121] demonstrated that low 25-OH Vit D levels were associated with symptomatic hemorrhage at initial clinical presentation. Furthermore, prospective cohort studies support a role for vitamin D supplementation in patients with CM.[116] In a study by Previch et al, 364 patients with spinal or cerebral CM were followed for 2018 patient-years. Those reporting vitamin D supplementation use had a 70% less chance of prospective hemorrhage than those not on supplementation, even after adjusting for age at presentation, brainstem location, and prior hemorrhage.[116] This study had limitations. It was an observational cohort study; thus, patients were not randomized. Doses of vitamin D vary, as do formulations of supplements. In addition, other factors which can affect vitamin D levels in patients (eg, obesity, sunlight exposure, and dietary intake) were not accounted for. Despite these strong cohort associations, there is to date no randomized clinical trial

evidence that vitamin D supplementation reduces hemorrhage risk or CM formation.

25-OH Vit D levels less than 20 are suboptimal for skeletal health. The optimal level for nonskeletal health is of debate. Guidelines suggest a daily intake of at least 600 to 800 IU of vitamin D daily. High-risk groups may need higher doses. With the CCM population, select seizure medications may reduce vitamin D in addition to living in in northern latitudes, body mass index >30, or less sunlight exposure.

REC-994

REC-994, an antioxidant, was found to restore endothelial dysfunction in vitro.[139] In September 2024, Recursion Pharmaceuticals reported that a phase II trial of REC-994 met its primary end point of safety and demonstrated encouraging trends in objective MRI-based exploratory efficacy measures.

Lifestyle Recommendations

Patients with CM not undergoing surgery may be anxious[53,54] and look for additional opportunities to reduce hemorrhage risk and morbidity from CM.

Physical Activity

Medications and activity that can increase potential seizure risk should be avoided in patients with CM and seizures.[140] No rigorous studies have been conducted to analyze activities pose theoretical risks in CM patients with and without seizures.[141] Joseph et al[142] did not find any relationship to physical activity at the time of hemorrhage due to CM, although this study was limited to mainly aerobic activity and light weight lifting.

Diet

The gut microbiome has been implicated in the pathogenesis of CM in animal models. It is believed that gut leakiness and reduced integrity of the gut mucosa leads to gram-negative gut bacteria entering the systemic circulation. The lipopolysaccharide of the gram-negative bacteria trigger the Toll-like receptor 4 inflammatory pathway leading to CM formation. Subsequently, Polster et al[143] demonstrated differences in the gut microbiomes using stool samples in those with CM vs no CM and could detect differences related to disease severity. Maintenance of the gut barrier is important to reduce leakiness of gram-negative bacteria (and lipopolysaccharide) into the systemic circulation. Although there are no clinical trials to assess the effectiveness of a diet low in processed foods (emulsifiers), it seems reasonable to recommend such a diet based on current national guidelines for general health and the potential to improve gut integrity.

Tobacco

The American Stroke Association recommends against tobacco use for ischemic stroke and general health. Several cohorts failed to demonstrate tobacco use as a risk for CM hemorrhage when used as a binary variable. One familial CM cohort showed that the number of pack years of tobacco use trended toward increased CM hemorrhage risk.[144] In the study assessing use of female hormonal agents and CM hemorrhage risk, the combination of female hormones and tobacco use raised the odds of CM hemorrhage compared with those with female hormones alone or those without female hormones. Therefore, it seems reasonable for general health and the potential influence on CM to recommend against tobacco use.

Alcohol

There are no observational cohort studies linking alcohol use with CM hemorrhage. However, data have been largely binary (use vs no use) without quantifying the amount. In some cohort studies, patients with CM presenting with hemorrhage had reported recent binge alcohol drinking.[121,122] It seems reasonable from general health and the potential risk of CM hemorrhage to recommend against excessive alcohol use and be consistent with American Heart Association guidelines regarding alcohol use.

High Blood Pressure

Although high blood pressure has been implicated as a risk factor for spontaneous ICHs, most cohort studies show no increase in CM hemorrhage risk in patients with a history of high blood pressure when assessed as a binary risk factor. This is likely because most spontaneous intracerebral hemorrhages are arterial bleeds susceptible to blood pressure fluctuation and autoregulation at the arteriole level. However, one study showed that a lower systolic blood pressure was significantly associated with a lower CM count and a trend toward reduced hemorrhage rates in familial CM patients.[145]

Mental Health

Several studies have reported that patients with CM have higher anxiety than the general population.[53,54] One cohort study has suggested a lower risk of CM hemorrhage in patients using SSRI medications than those without, even after adjusting for age, brainstem location, and prior hemorrhage.[116] Whether this finding is true, related to reduction in anxiety or related to the antithrombotic properties of SSRI, is not clear, and further research is necessary. In this population, at high risk for anxiety, an assessment of anxiety should be considered.

A summary of neurological recommendations is presented in Table 6, and other considerations regarding medical management of CMs are presented in **Supplemental Digital Content 1** (http://links.lww.com/NEU/E735).

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Supplemental digital content *is available for this article at neurosurgery-online.com.*

Supplemental Digital Content 1. **Supplementary Introduction**. Additional background on of Alliance to Cure Cavernous Malformation, and the original Consensus Guidelines, published in 2017. **Supplementary Methods**. Additional details about the literature search and writing procedures. **Supplementary Table 1**. Literature search terms for "Cavernous Malformation" and for the topics reviewed in this manuscript. **Supplementary Table 2**. Writing groups were mandated to cite all clinical trials, meta-analyses of trials, evidence-based guidelines, and systemic reviews published since 2014. This table includes the complete listing of those 234 mandated references. **Supplementary Epidemiology and Untreated Natural History**. Additional details on the rest factors for hemorrhage and untreated CM disease course. **Supplementary Considerations on Genetic Testing & Counseling**. Additional details on the genetic mechanism of inheritance, genetic variants, genotype-phenotype correlations, and the genetics of Sporadic CM. **Supplementary Imaging Considerations**. Additional information on advanced imaging techniques including Functional MRI, Diffusion Tensor Imaging, Dynamic Contrast-Enhanced perfusion imaging, and Quantitative Susceptibility Mapping. **Supplementary Table 3**. Reporting Consideration for Cavernous Malformations. **Supplementary Surgical Considerations**. Additional information on grading brainstem CMs, surgery related to epilepsy or spinal cord lesions, and special consideration for pediatric and older populations. **Supplementary Neurological Considerations**. Additional information on treating epilepsy in CM patients. **Supplementary References**. Additional references used to support findings reported in the supplementary content of this manuscript.