Meningoencephalitis of unknown etiology (MUE) is an umbrella term that encompasses a heterogeneous group of presumed autoimmune inflammatory brain diseases that commonly affect young to middle-aged dogs for which an underlying cause cannot be identified after extensive diagnostic investigations. Specific disease entities that are included under the designation of MUE include granulomatous meningoencephalomyelitis (GME), necrotizing meningoencephalitis (NME) of Pug and Maltese Dogs, necrotizing leukoencephalitis (NLE) of the Yorkshire terrier and other toy breeds, and eosinophilic meningoencephalitis (EME). Although the pathogenesis of each of the diseases is unknown, an immune-mediated basis is suspected in each and therefore is the common pathophysiologic denominator. Definitive diagnosis and thus differentiation of GME, NME, NLE, EME can currently only be accomplished via histopathologic examination of brain tissue as individual entities can share many potentially overlapping clinical and imaging features with each other and can also mimic other brain diseases, such as neoplasms. However, from a practical standpoint, MUE is most often presumptively diagnosed in dogs based on the following criteria:

1. Clinical signs of focal or multifocal brain or spinal cord disease;
2. Evidence of focal or multifocal, typically contrast-enhancing lesions on computed tomographic or magnetic resonance imaging scans of the brain; NME and NLE often have other topographically defining MRI features;
3. An inflammatory cerebrospinal fluid analysis (virtually any type of pleocytosis possible);
4. Negative titers and/or antigen/genetic tests for geographically prevalent infectious disease agents capable of causing meningoencephalitis.

CLINICOPATHOLOGIC FEATURES OF SPECIFIC MUE ENTITIES

Granulomatous Meningoencephalomyelitis (GME)

Some studies estimate that GME may represent up to 25% of canine CNS disease. GME most often presents as an acute onset, progressive, multifocal neurologic disease that has a propensity to female, toy and terrier breeds. However, both sexes and any breed may be affected. The mean age at diagnosis of neurological signs is about 4 years, but may range from 6 months to 12 years. The most frequent clinical signs reported include central vestibular, cerebellar, and cervical spinal cord signs, as well as seizures and visual deficits.

Although three forms of GME have been described, disseminated, focal and ocular, based on clinicopathologic abnormalities, this author makes no attempt to discriminate these, as dogs with all clinical forms often have imaging or pathological evidence of diffuse disease. The focal form of GME is most noteworthy in its ability to mimic intracranial neoplasia both clinically and on neuroradiological examinations (solitary macrogranulomatous lesion). The most common MRI findings include multiple hyperintense lesions on T2-weighted sequences scattered throughout the CNS white and grey matter. These lesions typically have irregular margins and demonstrate variable degrees of contrast enhancement. Neuropathologically
GME appears as an angiocentric, non-suppurative, mixed lymphoid encephalitis that predominately affects the white matter of the brain and spinal cord.

Studies of GME that include prognostic information report highly variable outcomes. It is clear that immunosuppressive treatment markedly improves the prognosis versus no treatment, with median survivals in treated dogs ranging from 1-3 years. It is also apparent that GME has a superior long-term prognosis compared to NME/NLE.

**Necrotizing Meningoencephalitis (NME) and Necrotizing Leukoencephalitis (NLE)**

NME and NLE are inflammatory disorders with a currently unknown etiology. Originally referred to as Pug Dog Encephalitis (NME) and Necrotizing Encephalitis of Yorkshire Terriers (NLE), respectively, these meningoencephalitides have now been reported in numerous breeds including the pug, Maltese terrier, Chihuahua, Yorkshire terrier, Pekingese, West Highland white terrier, Boston terrier, Japanese Spitz, and miniature Pinscher. To avoid confusion with breed-specific associations and given the considerable overlap that these entities can have clinically, on imaging examinations, and neuropathologically the author uses the term necrotizing encephalitis (NE) when diagnosing and referring to these conditions antemortem.

The onset of neurological signs associated with NE varies from six weeks to 10 years of age, and the median age of onset is typically younger (2 years) for dogs with NME versus NLE (4.5 years). Female, fawn-colored Pug Dogs younger than 7 years of age are more apt to develop NME than older, male and non-fawn individuals. Clinical signs referable to the forebrain predominate in dogs with NE, due to the bulk of lesions being distributed in prosencephalic structures. NLE is more likely than NME to cause brainstem signs but due to the multifocal nature the disease, any combination of signs is possible with either entity. Once present, interictal neurological dysfunction in cases of NE is typically rapidly progressive.

The distribution of lesions observed in NME and NLE on MRI can help with the imaging diagnoses. NME lesions typically appear as asymmetric, multifocal T2 hyperintense and T1 iso- to hypointense cerebral lesions affecting the grey and white matter, with variable contrast enhancement. Loss of grey/white matter demarcation may also be observed. In NLE, multiple, asymmetric forebrain lesions mainly affecting the subcortical white matter have been described, which may be cavitary, with relative sparing of the cerebral cortex. The neuropathologic features of both NME and NLE include non-suppurative meningoencephalitis and bilateral, asymmetric cerebral necrosis.

Recent research has reported that susceptibility to NME in Pugs is associated with the dog leukocyte antigen (DLA) region of dog chromosome 12. The association is near (or at) the region containing the DLA class II genes. Dogs that have two identical copies of the NME associated markers in this region are at significantly increased risk for NME in their lifetime compared to dogs that have only one or no copies of these markers (Table 1). This genetic test is available through multiple commercial laboratories.

**Table 1**

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
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<tbody>
<tr>
<td>N/N</td>
<td>Homozygous normal. No copies of the NME associated markers. These dogs have a low risk of developing NME.</td>
</tr>
<tr>
<td>N/S</td>
<td>Heterozygous susceptible. 1 copy of the NME associated markers. These dogs have a low risk of developing NME.</td>
</tr>
<tr>
<td>S/S</td>
<td>Homozygous susceptible. 2 copies of the NME susceptibility associated markers. These dogs are 12.75 times more likely to develop NME in their lifetime.</td>
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**Eosinophilic Meningoencephalitis (EME)**

EME differs from other MUE variants in that it has more of a propensity to affect larger breed dogs (15-20 kg) that are young to middle-aged. The most common neurological signs reported are consistent with diffuse forebrain disease including mentation changes, seizures, and visual deficits. However, a recent report also documented central vestibular signs in nearly 40% of dogs with EME. A significant proportion (>50%) of dogs with EME will have a peripheral eosinophilia in addition to the eosinophilic pleocytosis in CSF that is characteristic for this condition. MR findings in dogs with EME consistent most often of bilaterally symmetric cortical grey matter lesions and meningeal contrast enhancement. Another manner in which EME differs from other MUE variants is that a significant proportion of dogs with EME have long-term favorable responses to immunosuppressive treatment (median survival time 762 days) with 20-25% dogs being able to be weaned off medication entirely.

**MUE TREATMENT**

The inherent difficulty in establishing a definitive diagnosis of any of the disease entities that are included in MUE highlight several important factors regarding treatment. First, there are very few veterinary studies of dogs with confirmed cases of GME, NME, or NLE in which the efficacy of any treatment protocol has been established. Secondly, considering the diversity and heterogeneity of disease(s) in MUE, it is extremely difficult to objectively assess treatment. In the overwhelming majority of cases, GME, NLE, and NME should be considered relentlessly progressive and ultimately fatal diseases, and therefore often necessitate lifelong therapy and monitoring. Thus, expectations that include cure are largely unrealistic. However, aggressive treatment as outlined below can result in significant clinical improvement and prolonged periods of clinical remission. It is very difficult to predict which dogs may respond to treatment. However, a general rule of thumb for MUE cases is: 1) 33% of dogs will die or be euthanized within one week of diagnosis because of lack of response to therapy; 2) 33% will have a partial response to treatment (i.e. clinical improvement observed but obvious neurological disability persists), and 3) 33% return to normal or have subclinical deficits with treatment).

Immunosuppression remains the mainstay of MUE treatment, and can be accomplished in numerous ways, all of which will not be covered here. The most effective therapeutic regimens described to date typically involve combination therapies with corticosteroids and one or more additional immunosuppressive or immunomodulating agents. After diagnosis and critical review of MUE with the client, the author then reviews treatment options based on the following criteria in an attempt to identify a protocol that is ideally suited to each individual patient and owner:

- The perceived efficacy and expected prognosis associated with each specific protocol;
- The safety and tolerability of the drugs involved/adverse effects;
- Ease of administration and monitoring recommendations for each protocol; and
- The cost of each protocol.

It should be noted that the following treatment protocols with their associated prognoses are modified and composite reflections of previously published veterinary reports and the author's clinical experience.

**Protocol 1: Prednisone Monotherapy**
This protocol offers the advantages of being safe, conveniently administered by the owner at home, extremely economical, and requires virtually no specific procedures other than routine bloodwork every 6 months to monitor for adverse drug effects. Typical corticosteroid associated side effects (PU/PD, polyphagia, panting) should be anticipated. Prednisone is administered at 2 mg/kg/day PO for two weeks beyond the resolution of all clinical signs or until clinical signs fail to improve further for 2 consecutive weeks. The dose of prednisone is then tapered by 15-20% every 2 weeks until either the lowest alternate daily dose that maintains remission is attained or clinical relapse occurs. The primary disadvantage of prednisone monotherapy is that the majority of literature suggests it is not as efficacious compared to multidrug protocols, and side effects (iatrogenic hyperadrenocorticism) can be intolerable. However, in the author’s experience, dogs with MUE initially treated with prednisone monotherapy that fail to demonstrate clinical improvement may still benefit from intensifying the treatment as outlined in Protocols 2-6.

Protocol 2: Lomustine (CCNU) and Prednisone

Lomustine is a highly lipid-soluble nitrosurea alkylating agent that has been used in dogs as both a primary and rescue chemotherapeutic agent to treat lymphoma. Lomustine is administered at a dose of 60-70 mg/m² PO q 21 days in conjunction with prednisone as described in Protocol 1. Adverse effects of lomustine include myelosuppression, vomiting, and hepatotoxicity. The white blood cell nadir typically occurs 7-10 days after lomustine dosing. Monitoring of a CBC should occur at least prior to each lomustine dose. In the experience of the author, this protocol is economical compared to other combination therapies and well tolerated, but is not as efficacious as other multidrug protocols, with remissions lasting between 6-12 months. Most dogs receiving long-term lomustine therapy will develop cumulative thrombocytopenia or hepatotoxicity associated that will almost always necessitate discontinuation of treatment.

Protocol 3: Cytosine Arabinoside and Prednisone

Cytosine arabinoside (CA) is a synthetic nucleoside analog chemotherapeutic drug that competes with DNA polymerase in rapidly dividing cells, inhibits DNA repair, and has good penetration into the blood-brain barrier. Ideal CA dosing consists of administering 100 mg/m² IV as a CRI for 24 hours every three weeks in combination with prednisone. The IV CA protocol is pharmacologically superior to and has been shown to improve the response rate and survival compared to the subcutaneous route of CA administration. This CA treatment regimen is continued until clinical signs plateau or have resolved for 4 weeks, at which time the CA dosing interval is increased to every 6 weeks. Alopecia, dermatitis, myelosuppression, vomiting, and diarrhea are all possible side effects of CA usage. Because of its myelosuppressive potential, it is recommended that a CBC be performed to screen for myelosuppression prior to and 7-10 days after each CA administration. In the experience of the author and others, this protocol is well tolerated, rarely associated with clinically significant myelosuppression or gastrointestinal distress, and can result in prolonged periods of clinical remission.

Protocol 4: Cyclosporine and Prednisone

This is the author’s preferred method of MUE treatment, as it is easy to administer and monitor, very well tolerated, and has proven to be very efficacious. The author initiates
cyclosporine treatment at a dose of 5-7 mg/kg PO q 12hrs along with prednisone as described for Protocol 1. The most common adverse effects the author has noted with this protocol are dermatologic (alopecia, easy epilation of hair, or hair discoloration), and treatment is monitored with a CBC, biochemical profile and urinalysis performed monthly for the first 3 months and then every 3 months thereafter. Although therapeutic monitoring of cyclosporine concentrations is advocated by some clinicians, the author has found a poor correlation between serum cyclosporine concentrations and therapeutic efficacy, and currently only monitors cyclosporine concentrations if drug-related toxicity is suspected. In dogs with MUE that respond to this protocol, the daily cyclosporine dose can usually be reduced to the 3-5 mg/kg range to maintain remission. High serum concentrations of cyclosporine use can be associated with hepato- and nephrotoxicity, and long-term cyclosporine use may be a risk factor for the future development of malignant neoplasia. The primary disadvantage of this protocol is expense.

**Protocol 5: Procarbazine and Prednisone**

Procarbazine is a cytotoxic MAO inhibitor that is lipid soluble and readily crosses the blood-brain barrier. Procarbazine is initiated at a dose of 25-50 mg/m² PO q 24 hrs. Procarbazine tablets, available in 50 mg, require reformulation into a more dilute liquid formulation when being prescribed to small and toy breeds. Adverse effects of procarbazine include myelosuppression and hemorrhagic gastroenteritis. Dogs being treated with procarbazine should have a CBC performed weekly for the first month and then monthly thereafter. One study demonstrated that the median survival of dogs with MUE/GME treated with procarbazine and prednisone was 14 months, and that tapering or discontinuation of corticosteroid treatment was possible in a significant number of dogs treated. The major disadvantage of procarbazine is expense.

**Protocol 6: Leflunomide and Prednisone**

Leflunomide is an immunosuppressive agent most often used to prevent rejection of transplanted organs. Leflunomide is administered at a dose of 4-6 mg/kg/day PO in conjunction with prednisone as described in Protocol 1. The most common side effect seen by the author with this protocol are cutaneous drug eruptions. This protocol is also most commonly used by the author as rescue therapy in those dogs with MUE treated with other protocols that have a relapse of clinical signs that are refractory to dose intensification of their originally prescribed protocol.

**Selected References**


