



Practice parameter: The role of corticosteroids in the management of acute monosymptomatic optic neuritis

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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Optic neuritis (ON) is an inflammatory disorder of the optic nerve. Most cases are idiopathic or associated with MS. ON can be associated with a variety of systemic or ocular disorders and is the most common acute optic neuropathy in adults younger than 46 years. Among high-risk populations for MS, the incidence of ON is about 3 per 100,000 population per year, whereas in other areas the incidence is about 1 per 100,000 population per year.¹⁻¹³

Acute ON often presents as an isolated clinical event without contributory systemic abnormalities (monosymptomatic ON). Clinical features include periorbital pain, abnormal visual acuity and fields, reduced color vision, a relative afferent pupillary defect, and abnormal visual evoked potentials. The fundus may appear normal or demonstrate edema of the optic nerve head (papillitis).¹²⁻¹⁸ MRI white matter abnormalities identical to those seen in MS are found in 50 to 70% of monosymptomatic ON cases.¹⁹⁻²² The visual deficit of ON may worsen over 1 to 2 weeks and usually begins improving over the next month. Lack of improvement in visual function by 30 days is unusual.²³ However, most patients have some residual visual function deficit, even if visual acuity improves to 20/20.¹⁻¹⁸ Differential diagnosis includes compressive, ischemic, hereditary, toxic, or other inflammatory optic neuropathies (e.g., sarcoid). These conditions usually do not exhibit the same clinical pattern (table 1) or rate of recovery as monosymptomatic ON.¹⁻¹³

Treatment of monosymptomatic ON has included oral, retrobulbar, and IV steroids, immunoglobulin,

and acupuncture.²³⁻⁷⁷ Monosymptomatic acute ON is not rare and because the usefulness of oral prednisone in this disorder has recently been questioned,^{23,78-82} this practice parameter was developed to provide recommendations regarding the management of this common neurologic problem.

Evidence review. A literature search was conducted using Medline and Healthstar from 1966 to July 1, 1999. ON was cross-referenced with treatment and therapy. Citations earlier than 1966 were searched by cross-referencing techniques and an Index Medicus hand search. A total of 582 different citations dealing with ON and some aspect of therapy were identified and reviewed. Only literature published in well-disseminated journals dealing specifically with MS-related or idiopathic ON involving at least three patients was retained. Both retrospective and prospective data were reviewed. Citations were excluded when they simply described a small number of individual case reports or reviewed "ON" due to diseases such as sarcoid, lupus, anterior ischemic optic neuropathy, trauma, hereditary optic neuropathy, optic nerve compression, or other unrelated optic neuropathy.

Definitions for the classification of evidence.

Class I. Evidence provided by well-designed, randomized, controlled clinical trials, including overviews (meta-analyses) of such trials.

Class II. Evidence provided by well-designed observational studies with concurrent controls (e.g., case control and cohort studies).

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Table 1 Features of acute demyelinating monosymptomatic optic neuritis

1. Visual symptoms of recent onset
2. Progressive loss of vision over several days
3. Periocular pain particularly with eye movement
4. Abnormal visual acuity, color vision, and/or visual field consistent with optic neuropathy
5. Afferent pupillary defect in the eye with the abnormal function
6. Optic disc edema (due to papillitis) or a normal optic nerve without atrophy
7. Age in the later teens to mid-forties
8. No evidence of a contributory systemic illness associated with optic neuropathy with the exception of MS

Class III. Evidence provided by expert opinion, case series, case reports, and studies with historical controls.

All pertinent studies are listed in table 2.

Results. Several studies were identified, the largest of which was the National Eye Institute–sponsored Optic Neuritis Treatment Trial (ONTT).^{11,12,23,30-33,39,56-59,61-77,83-85} The ONTT enrolled 457 patients with acute ON, age 18 to 46 years, and followed them for 6 months or longer.²³ The study subsequently completed 5-year follow-up on a cohort of 388 ON patients with no history of MS.^{83,85}

ONTT patients were randomized into three treatment groups within 8 days of symptoms onset: 1) oral prednisone alone (1 mg/kg every day) for 14 days (oral treatment group); 2) IV methylprednisolone sodium succinate 250 mg four times daily (1000 mg/day) for 3 days in hospital, followed by oral prednisone (1 mg/kg every day) for 11 days as outpatient (IV treatment group or IVMP); or 3) oral placebo for 14 days (placebo group). The prednisone arm of the study was double-masked, whereas the IVMP arm was single-masked. The use of a placebo IV group was not included because study organizers could not justify, ethically or financially, hospitalizing patients for 3 days of sham IV therapy.^{65,84}

The study was designed to determine speed and level of recovery and complications of therapy. Visual acuity, visual fields, contrast sensitivity, and color vision were measured at study entry and at seven follow-up visits during the first 6 months, at 1 year, and then annually for 5 years. MRI was performed in nearly all patients at study entry. Lumbar puncture was optional and performed in 133 of 457 (29.1%) of the cohort.^{65,84} Two of 457 patients were eventually discovered to have compressive ON.

Oral prednisone at 1 mg/kg/day (previously the most common method of treating ON) failed to demonstrate any statistically significant improvement in the speed or degree of visual recovery compared to placebo.²³ The IV treatment group, by contrast, had significantly faster visual recovery than placebo over

the first 30 days ($p = 0.02$ and $p = 0.0001$ for the respective primary outcomes) but, after 6 months, there were no significant differences in visual acuity in the three treatment groups.²³ After 12 months of follow-up, visual acuity in the study eye was better than 20/20 in 69% and 20/200 or worse in only 3%.⁸⁶ The only predictor of a poor visual outcome was poor visual acuity at study entry. Of 160 eyes starting at 20/200 or worse, only 8 (5%) were still 20/200 or worse at 6 months.^{12,23,67}

Recurrent ON was greater in the group treated with oral prednisone alone than in the other two groups.^{23,61,62} Also by year 2, 30% of patients in the oral treatment group experienced at least one new attack of ON in *either eye* compared to 16% in the placebo group and 13% in the IV treatment group.^{23,71,75} This disparity among treatment groups continued throughout the 5-year follow-up period (41% recurrences in the prednisone treatment group and 25% in the IV and placebo groups; $p = 0.004$). Also, the ONTT noted that IVMP was associated with reduced risk of developing clinically definite MS in patients with an abnormal brain MRI at study entry and followed for 2 years compared to the two other treatment groups.^{71,83,87} These relationships between treatment and both recurrent ON and MS remain unexplained and controversial.^{78-82,88} Herishanu et al.⁴⁰ suggested that both recurrent ON and ON conversion to MS were greater following the use of IVMP compared to oral prednisone. This study, however, retrospectively evaluated a total of only 26 nonrandomized patients receiving no therapy, oral prednisone or IVMP, and, therefore, provides essentially Class III evidence of any such associations.

In the ONTT the therapeutic effect of the IVMP was no longer significant by the third year of follow-up (table 3).^{75,83} Among patients with a normal MRI, the 2-year rate of MS was so low that a benefit from IV treatment could not be established (see table 3).⁸³ The IV treatment arm of the ONTT was single masked.^{71,89} Patients or neurologists, using a detailed and standardized protocol months or years after therapy, are unlikely to have been biased in reporting attacks of demyelination in the IVMP group or in any of the other treatment groups.⁷⁶ All patient forms were reviewed without knowledge of the treatment arm by a neurologist experienced in MS.⁷⁶

Four other Class I and three other Class II corticosteroid treatment trials in ON that were relevant to this practice parameter were identified (see table 2).^{30-33,39,56-59} All were prospective, randomized, and placebo-controlled studies, although employing sample sizes considerably smaller than the ONTT. Thus, these studies lack the statistical power to exclude a therapeutic benefit to steroid treatment.⁹⁰ Several of these Class I studies report positive results. For example, Rawson et al. found that the speed of recovery in visual acuity was faster in patients receiving ACTH (40 units IM daily for 30 days; $p < 0.01$) compared to placebo over the first 30 days, although by 12 months there was no significant difference be-

Table 2 Studies of optic neuritis (ON) classified chronologically by level of evidence

Author and year published	Therapy used/study design	Cohort number	Outcome	Evidence class†
Glaser et al., ²⁴ 1952	IM ACTH 80 to 100 mg for 5 days; no control subjects	3	All three patients had improved VA	III
Rucker, ²⁷ 1956	IV ACTH vs other therapy; appears retrospective and not randomized	133	No significant difference	III
Giles and Isaacson, ²⁸ 1961	Steroids, vasodilator, typhoid H antigen; retrospective	Steroids, 48; vasodilator, 23; typhoid H antigen, 8	No significant difference in recovery	III
Oksala, ²⁹ 1964	Cortisone, antibiotics; retrospective	Antibiotics, 73; cortisone, 33	No significant difference	III
Rawson et al., 1966, ³⁰ 1969 ³¹	40 U IM ACTH vs placebo; randomized	ACTH, 25; placebo, 25	ACTH faster recovery but same VA by 12 mo	I
Bowden et al., ³² 1974	40 U ACTH for 30 days, placebo; randomized	ACTH IM, 27; placebo, 27	No significant VA difference at 2, 6, 12, or 24 mo	I
Gould et al., ³³ 1977	Retrolubular 40 mg triamcinolone, single masked control subjects (no placebo), 6-mo follow-up	Triamcinolone, 26; placebo, 28	Steroids gave faster recovery but VA the same at 6 mo	II
Spoor and Rockwell, ⁴¹ 1988	1 or 2 g IVMP; no control subjects	12	All improved some by 24 h	III
Herishanu et al., ⁴⁰ 1989	IVMP vs prednisone vs no therapy; not randomized, retrospective	26 divided into three groups	More conversion to MS with IVMP	III
Farris and Pickard, ⁴² 1990	IVMP with oral prednisone; no placebo	6	Rapid and near-total recovery	III
Mehdorn, ³⁴ 1990	1 g IVMP vs mannitol	4	Quick recovery in both groups	III
Trauzettel-Klosinski et al., ³⁹ 1991	100 mg/d oral MP vs thiamine (as placebo); partially randomized, mixed design	Thiamine, 36; oral MP, 14	MP improved faster; placebo same as oral MP at 12 mo	II
van Engelen et al., ³⁵ 1992	0.4 mg/kg/d IVIg for 5 d then every 2 wk for 1 y, uncontrolled	5	Improved VA at 3 mo; maintained for >1 y	III
Gerling and Kommerell, ⁴⁴ 1992	1 g IVMP/d × five; no control group	17 patients: 15 unilateral, 2 bilateral; therapy started 1 to 70 days after ON	Rapid recovery in 12 of 17 patients during treatment period only	III
Beck et al., ^{23,71,83} 1992, 1993, 1997	Prednisone 1 mg/kg/11 d; IVMP g/d × 3 followed by prednisone; placebo; prospective, randomized, placebo controlled (for prednisone only)	Placebo, 150; IVMP, 151; prednisone, 156; therapy within 8 days (5-year MS risk assessment: placebo, 126; IVMP, 134; oral prednisone, 129)	More ON recurrence with prednisone than placebo; IVMP speeds recovery; reduced rate of onset of MS for 2 y when MRI abnormal	I/prednisone II/methylprednisolone
Alejandro et al., ⁵⁵ 1994	Oral prednisone 1 mg/kg vs IVMP 500 mg every 8 h × 10	IVMP, 8; prednisone, 8	No differences between the groups regarding clinical outcome; very small sample size	III
Toczolowski et al., ⁵³ 1995	Oral steroids vs peribulbar vs IVMP; no control subjects; not randomized	98	IVMP more effective than other methods in regaining vision	III
Koraszewska-Matuszewska et al., ⁵⁴ 1995	Many steroid types; unclear control group; retrospective	110 children ages 2 to 18 y	“Recovery” of VA in 75% of patients	III
Kapoor et al., ⁵⁶ 1998	IVMP vs placebo; randomized	IVMP, 33; placebo, 33; all had optic canal MRI lesions	Faster (nonsignificant) time to recovery for IVMP vs placebo	I
Wakakura et al., ¹³ 1999	IVMP vs placebo (mecobalamin); randomized prospective; not specifically listed as masked assessment	IVMP, 33; placebo, 33	IVMP faster recovery but the same at 12 wk and 1 y	II
Sellebjerg et al., ⁵⁹ 1999	Oral MP 500 mg vs placebo	Oral MP, 30; placebo, 30	Oral MP faster recovery but no difference at 8 wk	I

* As defined by the American Academy of Neurology Quality Standards Subcommittee.

† Class I = well-designed, prospective, randomized, placebo-controlled study; Class II = well-designed, observational studies; Class III = expert opinion, case series, and studies with historical control subjects.

VA = visual acuity; MP = methylprednisolone; Ig = immunoglobulin.

tween groups.^{30,31} Bowden et al.³² similarly demonstrated that visual acuity was the same at 12 months in patients treated with either ACTH (40 units IM daily for 30 days) or placebo. Kapoor et al. showed no effect of IVMP (1000 mg/d × 3 days) compared to placebo on the visual outcome at 6 months in 66 individu-

als with ON lesions involving the optic canal.⁵⁶ Sellebjerg et al. studied 60 patients⁵⁹ using either 500 mg of oral methylprednisolone daily for 5 days with a 10-day taper or placebo. They reported that there was an increased speed of visual recovery in the treated group ($p = 0.008$) but no long-term benefit compared

Table 3 Cumulative probability of patients with clinically definite MS after specific time intervals by treatment group⁸³

Time after entry	Treatment group, %		
	IV methylprednisolone,* n = 133	Prednisone,† n = 129	Placebo, n = 126
6 mo	3	7	7
1 y	6	10	13
2 y	8	16	18
3 y	18	25	21
4 y	25	28	26
5 y	27	32	31

Time after entry	Relative risk (95% CI)	p Value
2 y		
IV vs placebo	0.34 (0.16–0.74)	0.006
Prednisone vs placebo	0.90 (0.48–1.71)	0.75
5 y		
IV vs placebo	0.81 (0.50–1.30)	0.38
Prednisone vs placebo	1.05 (0.67–1.65)	0.85

Excludes patients with probable or definite MS at study entry.

* IV therapy with methylprednisolone, 250 mg every 6 h × 3 d followed by prednisone treatment.

† Oral prednisone therapy 1 mg/kg/d × 11 d followed by 4 d taper.

to placebo. There was no increase in recurrence of ON at 1 year using oral methylprednisolone; however, they noted that the number of patients was too low to rule out an effect on subsequent disease activity.⁵⁹

Three Class II studies were noted. Gould et al. found that ON treated with a single dose of retrobulbar triamcinolone (40 mg) was associated with nonsignificant increase in the speed of visual recovery but resulted in no benefit compared to placebo at 12 months.³³ In 1999, Wakakura et al. evaluated 66 patients with optic neuritis treated with either 1000 mg IVMP for 3 days or mecobalamin (500 mg/day) and found that IVMP improved the speed of visual recovery in the first several weeks ($p < 0.05$) but that visual function at 12 weeks and 1 year did not differ between the two groups.^{13,58} Another oral methylprednisolone study has also been reported. The Tübingen study tested 50 patients,^{39,57} 14 of whom were treated patients with 100 mg of oral methylprednisolone for 3 days, subsequently tapering the dose by 20 mg every 3 days thereafter. At 4 weeks the treated group had a 61% better visual outcome (nearly normal function) compared to placebo (thiamine), although this was not statistically significant. By 12 months, however, no such difference was apparent.

Thirteen Class III studies were also identified (see table 2). These included reports from the early 1950s dealing with glucocorticoid treatment of ON.^{24,27} All of these studies had serious methodologic flaws related to very low patient numbers,⁹⁰ retrospective analysis, no randomization, or lack of placebo

control.^{24,27-29,34,35,40-42,44,53-55} In a 1988 publication, Spoor and Rockwell showed rapid recovery of vision (some within 24 hours) in 12 patients given 1 to 2 g of IVMP. This study was neither randomized nor placebo-controlled.⁴¹ A study by Alejandro et al. in 1994 looked at eight patients given IVMP versus eight patients treated with oral prednisone and found no difference between groups.⁵⁵ Other studies are listed in table 2.

There are also several studies reviewing the prognostic value of MRI and CSF in determining the relative risk of developing MS after ON.^{20,60,83,91} However, an in-depth analysis of that work is beyond the scope of this practice parameter.

Recommendations. Definitions for the strength of recommendations were based on the following criteria:

Standard: A principle for patient management that reflects a high degree of clinical certainty (usually this requires Class I evidence that directly addresses the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).

Guideline: A recommendation for patient management that reflects moderate clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence).

Practice Option: A strategy for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion).

Practice Advisory: A practice recommendation for emerging and/or newly approved therapies or technologies based on evidence from at least one Class I study. The evidence may demonstrate only a modest statistical effect or limited (partial) clinical response, or significant cost–benefit questions may exist. Substantial (or potential) disagreement among practitioners or between payers and practitioners may exist.

Acute monosymptomatic ON recommendations.

Oral prednisone in doses of 1 mg/kg/day has no demonstrated efficacy in the recovery of visual function in acute monosymptomatic ON, and therefore is of no proven value in treating this disorder. *Standard*

Higher dose oral or parenteral methylprednisolone or ACTH may hasten the speed and degree of recovery of visual function in persons with acute monosymptomatic ON. There is, however, no evidence of long-term benefit for visual function. The decision to use these medications to speed recovery but not to improve ultimate visual outcome should therefore be based on other non-evidence–based factors such as quality of life, risk to the patient, visual function in the fellow eye, or other factors that the clinician deems appropriate. *Guideline*

Recommendations for future research. Several management issues still lack evidence for specific recommendations: 1) whether corticosteroid treatment is beneficial in patients whose symptom duration is longer than 8 days; 2) whether larger doses of corticosteroids are more effective than lower doses;

3) what the optimal corticosteroid regimen is; 4) whether the observed increased ON recurrence rate associated with oral prednisone is also observed in MS attacks; and 5) whether high-dose methylprednisolone given periodically will improve the prognosis for patients with MS.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Appendix

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