

**IJMSC** Volume 4, Issue 4  
Dec-Winter 2002

**Editorial**

Resources for Clinical Measurement in Multiple Sclerosis

**Robert M. Herndon, MD**

Robert M. Herndon is Professor of Neurology at the University of Mississippi Medical Center and Editor-in-Chief of the International Journal of MS Care.



Advances in the care and treatment of those with multiple sclerosis (MS) depend on clinical research. There has been an exponential increase in clinical research over the past few decades, driven by the development and availability of new drugs and improved tools for use in clinical trials. Most of the trials have been directed at treatment of the disease process, but increasingly, clinical trials and outcomes research studies are being conducted to improve symptom management, which can have a significant impact on the quality of life of those with MS. These are important studies and have required the development of a host of new measurement tools, some of which are well validated while others are not yet adequately validated. They vary greatly in complexity and in the time required for their completion. Measures range from counting new exacerbations to quantitative measures such as timed ambulation, nine-hole peg test, and detailed cognitive testing. Selection of the appropriate scale or measurement tool is among the most important steps in planning clinical research.

Both clinical trials and outcomes research require efficient and effective measurement tools. Selecting the appropriate tool is becoming easier as new resources become available. There are a variety of sources from which information on neurologic measurement and scales can be obtained. Sources include *Measurement in Neurological Rehabilitation* by Derick Wade (Oxford Univ. Press, 1992) and *Handbook of Neurological Rating Scales* by Robert M. Herndon (Demos Vermande [now Demos], 1997). Both of these are helpful resources that contain useful information. Unfortunately, both are now a bit out of date and do not include some of the newer measures. A new source has recently appeared online at the National MS Society Web site (<http://www.nationalmssociety.org>). This Web site has a listing of most of the scales used in MS research and includes the date the information on each scale was last revised. While the focus is necessarily somewhat narrower than the two books mentioned above, it is an excellent site with appropriate citations. Those interested in measuring almost any aspect of MS would do well to visit the site, which will assist them in selecting the best scale for measuring almost any MS-related function. Coverage ranges from the Kurtzke extended disability status scale and the MS Functional Composite to bladder and bowel scales and psychological tests. The individual scales are discussed in considerable detail and primary sources are provided..

It is important to use scales for the purpose(s) for which they were designed; other purposes require adequate validation. There are excellent discussions of types of validity in the books cited. Additional information on designing clinical trials, including the importance of blinded patient evaluation and details of trial planning, can be obtained from any one of the numerous books on clinical trials, including Good Practice of Clinical Trials by A. Spriet and T. Dupin-Spriet (Karger, 1994), Clinical Trials: Design, Conduct and Analysis by C.L. Meinert (Oxford Univ. Press, 1986), and several more recent books on the subject. Time spent in carefully planning a trial is well spent as changes are difficult to make once a trial has begun and a poorly designed trial results in a great deal of wasted effort.

## Report of the Consensus Panel on the New International Panel Guidelines for Diagnosis of MS

**Robert M. Herndon, MD; Patricia K. Coyle, MD; Thomas J. Murray, MD; and Jerry S. Wolinsky, MD, for the Consensus Panel**

Robert M. Herndon is Professor of Neurology at the University of Mississippi Medical Center and Editor-in-Chief of the International Journal of MS Care. Patricia K. Coyle is Professor of Neurology and Director of the Stony Brook MS Comprehensive Care Center at Stony Brook University in New York. Thomas J. Murray is Professor of Medical Humanities at Dalhousie University and Director of the Dalhousie MS Research Unit, Halifax, Nova Scotia. Jerry S. Wolinsky is a Professor in the Department of Neurology at the University of Texas Health Science Center in Houston.

### Abstract

*The new international panel guidelines for diagnosis of multiple sclerosis (MS) raised a number of concerns regarding their use and application, particularly in relation to their impact on treatment issues and options. As a result, a consensus panel composed primarily of North American neurologists with inclusion of several members from the International Panel was convened in Fort Worth, Texas, November 30 to December 2, 2001, to discuss these concerns, resulting in the following consensus statement regarding the guidelines and their appropriate use*

Suggested Citation: . Report of the Consensus Panel on the New International Panel Guidelines for Diagnosis of M. Herndon, R et al. *Int J MS Care*. [serial on-line]. 2002;4:(4).

---

Publication of the new International Panel (IP) guidelines for diagnosis of MS by McDonald et al<sup>1</sup> has raised some concerns in the North American neurological community. These concerns relate to the general complexity of the guidelines, their potential use as treatment rules, and, in particular, the complexity of the magnetic resonance imaging (MRI) criteria for dissemination in time and space and for the diagnosis of primary progressive MS (PPMS). Because of these concerns, the Consortium of MS Centers (CMSC) convened a consensus conference to review and discuss the guidelines and their interpretation. The conference met November 30 to December 2, 2001, in Fort Worth, Texas. The following consensus statements were endorsed during the conference:

- The IP guidelines represent a significant advance over previous criteria<sup>2,3</sup> in that they incorporate MRI criteria to allow earlier, more accurate diagnosis.
- The IP guidelines are for diagnosis only. They are not designed to make treatment decisions or to determine prognosis.
- Since the new McDonald criteria are only guidelines, diagnosis ultimately depends on a physician (preferably a neurologist) skilled and knowledgeable in the diagnosis and management of patients with MS.
- MRI should be part of the diagnostic evaluation for MS in all cases in Canada, the United States, and wherever the technology is available, unless a contraindication exists.

- Steps are being taken to standardize MRI acquisition, interpretation, and reporting. Similar steps should be taken to standardize other paraclinical tests used in the diagnosis of MS, such as cerebrospinal fluid (CSF) assays.

- In the next few years, new information should allow refinement of the IP guidelines to improve their ease of application and their sensitivity without compromising specificity.

It is recognized that the IP guidelines need to be clarified in certain areas where evidence is lacking. Further research should establish:

- Minimal MRI criteria to diagnose PPMS.
- Appropriate CSF requirements for PPMS.
- The validity of defining MS on the basis of MRI characteristics alone or at first attack.
- The optimal protocol for follow-up MRI exams when required for diagnosis.

The conference members recognize that primary evidence exists to support disease-modifying therapy in certain patients presenting with their first demyelinating event (referred to by the IP as “possible MS”).<sup>4,5</sup> Further research is needed to identify factors in these patients that predict tissue destruction and future disability.

### Consensus Statements

The IP guidelines represent a significant advance over previous criteria in that they incorporate MRI criteria to allow earlier, more accurate diagnosis.

Although the new MRI criteria were generally regarded as difficult to apply, they do allow MRI to be used to define dissemination in space and (with a repeat MRI) dissemination in time. Their difficulty in application refers in particular to the fact that most radiologists do not report lesion distribution and most generalists are not sufficiently conversant with the details of MRI to do it themselves. Most conference members saw a need to simplify the MRI criteria. Since the criteria are evidence based, simplification will require additional research.

The IP guidelines are for diagnosis only. They are not designed to make treatment decisions or to determine prognosis.

Conference members agree that there are individuals who clearly have MS and who will not meet IP criteria at the time diagnosis is considered. Some of these individuals will have findings that suggest aggressive disease. In other cases, individuals who meet criteria may have very few lesions, several years between attacks, no significant clinical residual, and a benign MRI picture. Because of this, most panel members thought that treatment decisions should not be based on the diagnostic criteria. These concerns are also discussed below with regard to the final consensus statement.

Since the new McDonald criteria are only guidelines, the diagnosis ultimately depends on a physician (preferably a neurologist) skilled and knowledgeable in the diagnosis and management of patients with MS.

Diagnostic criteria will change over time as technology and knowledge advance. There are individuals who have MS and who do not meet the guidelines. At the time of the first attack, no one meets criteria for definite MS, but it is clear that many already have the disease. In addition, the caveat “no better explanation” requires broad neurologic knowledge, including familiarity with diseases that mimic MS. Conference members recognize that there are some nonneurologists who are skilled in the diagnosis of MS, but they are few in number. In practice, a neurologist usually makes the diagnosis. In particular, it was agreed that a neurologist with expertise in MS should evaluate difficult and atypical cases.

MRI should be part of the diagnostic evaluation for MS in all cases in Canada, the United States, and wherever the technology is available, unless a contraindication exists.

MS has many mimics. A number of these are most easily picked up on MRI. While it is possible to diagnose MS without MRI, the number of errors in diagnosis is reduced markedly when both clinical and MRI studies are available to the diagnosing physician. Additionally, the MRI burden of disease on T2 or fluid-attenuated inversion recovery (FLAIR) images provides useful prognostic information. For this reason the conference members considered that MRI of the brain should always be included as part of the work-up and evaluation, except in those situations where there are contraindications. The conference members realize that there are parts of the world in which MRI is not available. In these areas diagnosis must be made without MRI. In countries where the technology is available, the conference members considered MRI to be an essential part of evaluation and diagnosis.

Steps are being taken to standardize MRI acquisition, interpretation, and reporting. Similar steps should be taken to standardize other paraclinical tests used in the diagnosis of MS (such as CSF assays).

The CMSC has convened a panel to standardize acquisition, interpretation, and reporting of MRI results in MS. Such standardization will facilitate use of the IP MRI criteria and make them easier to apply, therefore making MRI more useful to neurologists. Similar standardization is also needed in other areas. Assessment of CSF needs further standardization. For example, isoelectric focusing is much more sensitive than agarose gel electrophoresis in detecting oligoclonal bands. Some CSF specimens that are reported as negative are actually positive when assessed by more sensitive techniques.

The IP did not accept somatosensory evoked potentials (SSEPs) in their criteria. These tests lack standardization in technique and interpretation. Many neurologists believe that SSEPs can be used to objectify sensory complaints, thus making purely sensory symptoms into an objective finding useful in diagnosis.

New information should allow refinement of the IP guidelines to improve their ease of application and their sensitivity without compromising specificity.

It is now more than 17 years since the Washington panel was convened and the diagnostic criteria revised. The new IP criteria represent an advance, but the conference members agreed that we should not wait years to revisit and revise the criteria. The revision process should be recurring with appropriate updates based on new technology and new research findings. Ultimately, a biological marker may make these criteria obsolete. Until that time, there must be periodic revisions to include the results of new research. The conference members recognized that the criteria were designed and intended to have high specificity at the cost of sensitivity. The conference members agreed that high specificity is more important than sensitivity in these criteria.

## Areas for Clarifications

### **Minimal MRI criteria to diagnose PPMS**

Diagnosis of PPMS remains difficult. The IP criteria are highly insensitive, and it is clear that some clinically typical cases will not meet the formal MRI criteria. Additional information is likely to become available as results of current PPMS clinical trials are published. Further research is needed to help clinicians differentiate PPMS from spinal cord degenerative disease and other mimics. This remains one of the most difficult diagnostic areas in MS, and more information is needed if we are to avoid the pitfalls of underdiagnosis and misdiagnosis. This is not a pressing issue at present since there are no approved treatments for PPMS, but it will become urgent if useful disease therapy is developed.

### **Appropriate CSF requirements for PPMSS**

The IP criteria require abnormal CSF. Given the unsatisfactory state of CSF testing, this presents difficulty. Isoelectric focusing techniques to detect oligoclonal bands need to become standard to increase the diagnostic sensitivity of CSF testing for PPMSS. Even using this more sensitive technique, some patients with PPMSS have normal CSF. There must be a way to diagnose PPMSS in patients with normal CSF while maintaining the current level of diagnostic specificity.

### **Validity of defining MS on the basis of MRI characteristics alone or at first attack**

The diagnosis of MS remains clinical. Ancillary tests including MRI assist in the diagnosis, but individuals must meet criteria for dissemination in time and location to be diagnosed. There are some who believe that, if certain fairly rigid criteria are met, MS can be diagnosed on the basis of MRI in clinically isolated syndromes such as optic neuritis or transverse myelitis. If MS can be diagnosed on the basis of MRI in this situation, either alone or with the addition of MR spectroscopy or other developing techniques, the validity of the approach must be established.

### **Optimal protocol for follow-up MRI exams when required for diagnosis**

The new diagnostic criteria accept the occurrence of new T2 lesions or new enhancing lesions appearing on MRI, after a minimum interval of three months, as acceptable evidence for dissemination in time. This minimum interval needs to be further validated. In addition, the optimal interval that provides maximum yield from minimum repeat MRI, and thus minimum cost, needs to be defined. Should a repeat be done every three months until a diagnosis is made? That would be unnecessarily expensive in relatively inactive cases. Perhaps MRI at three and six months then no further tests unless there is clinical evidence of disease activity would be reasonable. Unfortunately, we do not have the data to make firm recommendations at the present time. Data from serial MRI studies that have been done might provide information to make such recommendations, though selection criteria for such studies may limit their generalizability.

Finally, the conference members emphasized that the diagnostic criteria were not designed to provide prognostic information or to determine need for treatment. There is class I evidence from both the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention Study (CHAMPS) and the Early Treatment of MS Study (ETOMS) trials regarding the utility of treating selected patients at the time of their first attack. The numbers of misdiagnosed patients in these trials were minimal and the benefits of therapy demonstrated. These patients were not required to meet the IP criteria for diagnosis. In other specialties that treat chronic diseases such as lupus erythematosus and rheumatoid arthritis, many patients are treated before the diagnosis is firm if certain criteria are met. MS is no exception, and treatment should not be withheld unnecessarily in patients with the disease who do not meet current formal diagnostic criteria. The vast majority, though not necessarily all patients, who meet IP diagnostic criteria for relapsing MS deserve access to disease-modifying therapies.

## **REFERENCES**

1. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the Diagnosis of Multiple Sclerosis. *Ann Neurol.* 2001;50:121-127.
2. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol.* 1983;13:227-231.
3. Schumacher FA, Beeve GW, Kibler RF, et al. Problems of experimental trials of therapy in multiple sclerosis: report by the panel on the evaluation of experimental trials in multiple sclerosis. *Ann N Y Acad Sci.* 1965;122:552-568.

4. Jacobs LD, Beck RW, Simon JH, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. CHAMPS Study Group. *N Engl J Med*. 2000;343:898-904.

5. Comi G, Filippi M, Barkhof F, et al. Effect of early interferon treatment on conversion to definite multiple sclerosis: a randomised study. *Lancet*. 2001;357:1576-1582.

*Organizing committee: Robert M. Herndon, MD; Patricia K. Coyle, MD; Mark Freedman, MD; Craig Smith, MD; Richard Rudick, MD; and Jerry S. Wolinsky, MD.*

*Conference Speakers: Richard Rudick, MD; Jerry S. Wolinsky, MD; Mark Freedman, MD; Eric Eggenberger, DO; Revere Kinkle, MD; Geert Lycklama; David Miller, MD; Donald Paty, MD; and Jack Simon, MD.*

*Attendees: Douglas Arnold, MD; Robert W. Baumhelfner, MD; Gary Birnbaum, MD; Donna Jo Blake, MD; James Bowen, MD; Jack Burks, MD; Jonathan Carter, MD; Stanley Cohan, MD, PhD; Bruce Cohen, MD; Arthur Cyrtyrn, MD; David Dawson, MD; John Greenlee, MD; Jeffrey Greenstein, MD; Charles Guttman, MD; Jodie Haselkorn, MD, MPH; Stanley Hashimoto, MD, FRCPC; John Huddlestone, MD; Norman Kachuck, MD; Michael Kaufman, MD; Pierre Ketelaer, MD; Mariko Kita, MD; R. John Leigh, MD; Thomas Leist, MD; Robert Lisak, MD; D. Joanne Lynn, MD; Michele Mass, MD; Micheline McCarthy, MD, PhD; Luanne Metz, MD, FRCPC; James Q. Miller, MD; Jock Murray, OC, MD, FRCPC, MACP; Pamela New, MD; Hillel Panitch, MD; Michael Racke, MD; Anthony Reder, MD; Loren Rolak, MD; Jay Rosenberg, MD; Vernon Rowe, MD; Steven Schwid, MD; William Sheremata, MD; James Simsarian, MD; Dusan Stefanoski, MD; Lael Stone, MD; Anthony Traboulsee, MD, FRCPC; Jay Tsurda, MD; William Tyor, MD; Timothy Vollmer, MD; Bianca Weinstock-Guttman, MD; and Ernest Willoughby, MD.*

## A Randomized Controlled Safety Trial of Interferon beta-1a and Oral Cyclophosphamide in MS

**Michael Kaufman, MD; H. James Norton, PhD; and Gerald Sonnenfeld, PhD**

Michael Kaufman, MD, is Director of the MS Center, and H. James Norton, PhD, is Director of Biostatistics, both at the Carolinas Medical Center, Charlotte, North Carolina. Gerald Sonnenfeld, PhD, is Chairman, Department of Microbiology, Biochemistry and Immunology, Morehouse School of Medicine, Atlanta, Georgia.

### Abstract

*We evaluated the safety of adding oral cyclophosphamide to interferon beta-1a (IFNβ-1a; Avonex™) in a placebo-controlled randomized study of 24 patients with multiple sclerosis (MS). The clinical course was monitored during nine months of treatment. Treated patients tolerated 150 to 200 mg/m<sup>2</sup> of weekly administered cyclophosphamide and IFNβ-1a with few reported side effects. We conclude that oral cyclophosphamide can be added safely to IFNβ-1a without intolerable acute side effects. One death unrelated to treatment occurred. Cholecystitis and a benign breast mass both developed in a single cyclophosphamide-treated participant. Leukopenia and lymphopenia were observed in treated participants. Longer, larger trials testing the efficacy of cyclophosphamide may be appropriate for some individuals with breakthrough disease activity while taking IFNβ-1a.*

Suggested Citation: A Randomized Controlled Safety Trial of Interferon beta-1a and Oral Cyclophosphamide in MS. Kaufman, M. et al. *Int J MS Care* [serial on-line]. 2002;4:(4).

---

Interferon beta-1a (IFNβ-1a) is an effective treatment for relapsing forms of multiple sclerosis (MS).<sup>1-3</sup> Cyclophosphamide (CYP; Cytoxan™) is an alkylating agent and a radiomimetic, which is non-cell-cycle specific and is effective on both dividing and nondividing cells. Some preliminary trials using intravenous cyclophosphamide have shown a modest benefit in slowing disability of patients with progressive MS,<sup>4,5</sup> although one large trial did not demonstrate sustained efficacy.<sup>6</sup> Two small studies have suggested that the combination of intravenous CYP and IFNβ for up to 18 months may benefit patients with rapidly worsening MS.<sup>7,8</sup> While CYP could merely deplete leukocytes, it may also have immunomodulatory effects in MS. This is supported by studies showing reduction of interleukin-12 (IL-12) production<sup>9</sup> and promotion of type 2 cytokine-producing T cells.<sup>10</sup> If the effects of IFNβ-1a and CYP were additive or synergistic, better control of MS would be achieved by their concurrent use. Because CYP can be given conveniently and inexpensively by mouth, we evaluated its oral use in combination with IFNβ-1a (Avonex™).

### METHODS

The study was conducted at Carolinas Medical Center, Charlotte, North Carolina, between April 1999 and October 2000. Carolinas Medical Center Institutional Review Board approved the protocol, and all participants received a copy of the informed consent that included precise

information about the possibility of sterility and chemical menopause. No tolerance of clinical disease activity was the basis for recruiting patients. All patients who met the inclusion criteria within the nine-month recruitment period and gave consent were included in the study. Inclusion criteria were ages 21 to 65, relapsing or secondary progressive MS, Expanded Disability Status Scale (EDSS) score of 1.5 to 6.5, continuous treatment with IFN $\beta$ -1a for six months or longer, and clinical disease activity. Clinical disease activity was defined as at least one relapse in the preceding two years or objective disease progression while being treated with IFN $\beta$ -1a. The study duration was chosen with the expectation that the short-term safety of combination therapy and differences in cytokine production could be evaluated within nine months. Long-term safety could not be assessed in a placebo-controlled trial.

A computer-generated random number table was used to assign participants to add either placebo CYP (n = 13) or CYP (n = 11) to ongoing IFN $\beta$ -1a treatment. A compounding pharmacy made the placebo, distributed both treatments, and recorded which treatment was given to participants.

Therapy was initiated at a dose between 125 and 150 mg/m<sup>2</sup>, given once weekly on the fourth or fifth day after the IFN $\beta$ -1a injection. The dosage was increased monthly to a maximum of approximately 250 mg/m<sup>2</sup> or 500 mg weekly, whichever resulted in the lower weekly dose. Previous experience in our center had shown that the usual maximum tolerated dose of CYP fell within this range. The dose was reduced by predetermined rules based upon abnormalities of monthly white blood counts, liver function tests, and urine analyses (Table 1). As far as possible, each participant randomized to CYP was paired with another subject randomized to placebo, and the dosage of study drug was adjusted in parallel for both. All participants were encouraged to take 30 grains of sodium bicarbonate four times orally on the day of therapy to alkalinize the urine and reduce bladder wall irritation. Exacerbations were treated with intravenous methylprednisolone at the discretion of the physician.

**Table 1**  
**Rules for cyclophosphamide dose reduction**

Lab test	Reduce by 50 mg/m <sup>2</sup>	Stop
Leukocytes	< 1,800, > 1,300	< 1,300
Lymphocytes	< 400, > 250	< 250
Platelets	< 100,000, > 75,000	< 75,000
Hemoglobin	Fall of 1.5 but > 9.5	< 9.5
Urine hgb (nonmenstruating)	Trace to 1+	> 1+
AST	> 1.5 ULN, < 2.5 ULN	> 2.5 ULN
Alkaline phosphatase	> 1.5 ULN, < 2.0 ULN	> 2.0 ULN
Bilirubin	> 1.5 ULN, < 2.0 ULN	> 2.0 ULN
Creatinine	> 1.5 ULN, < 2.0 ULN	> 2.0 ULN

Hgb, hemoglobin

AST, aspartate transaminase

ULN, upper limit of normal

The primary outcome measure was the safety of concurrent administration of CYP and IFN $\beta$ -1a. The combination was assessed for possible accelerated deterioration in clinical neurological status. The physician determined EDSS scores at months 0, 3, 6, and 9, and within seven days of possible exacerbations; any exacerbations were recorded. Twice during the baseline phase and every three months thereafter, a technician, blinded to the treatment, performed a Multiple Sclerosis Functional Composite (MSFC) test. The difference in the number of adverse experiences between the two treatment arms was followed. Participants reported adverse

events that were tallied by the research coordinator at monthly visits. An independent neurologist reviewed all serious adverse events and examined safety data when half of all participants had completed six months of the trial.

A surrogate end point using assays of cytokine production was explored using cells harvested monthly. IL-4 and IL-10 (TH2 cytokines) and IL-2 and IFN-g (TH1 cytokines) were measured both in plasma and in mitogen (Con-A)-stimulated peripheral blood leukocytes (PBLs) using commercially available ELISA assay kits.

Since CYP tablets cannot be crushed and placebo tablets with a similar speckled pattern were unavailable, disguising CYP tablets was impossible. Therefore, the study coordinator was unblinded by counting unused pills when assessing compliance of participants. The physician may have been unblinded by review of laboratory values and adverse experiences. The success of blinding for the MSFC technician, participants, and the physician was determined by questionnaire at the end of the study.

Descriptive statistics were calculated using standard techniques. When data were not normally distributed between the two groups, the Wilcoxon rank sum test was employed. Nominal scale data were compared using a Fisher exact test. A P value of less than .05 was considered statistically significant. Z-scores were calculated in comparison to the MSFC data set based on the Multiple Sclerosis Task Force database and used the method outlined in Administration and Scoring Manual for the Multiple Sclerosis Functional Composite Measure.<sup>11</sup>

## RESULTS

Both groups were balanced with respect to age, sex, and the presence of relapses in the previous two years. The CYP group was more disabled than the placebo group at entry assessed by EDSS score and MSFC Z-score. This did not reach significance due to the small sample size (Table 2).

**Table 2**  
**Baseline characteristics**

	Cyclophosphamide-treated	Placebo-treated	P value
Age	44.2 ± 10.5 years	43.2 ± 7.6 years	NS
% Female	80% (8/10)	77% (10/13)	NS
% With relapses	70% (7/10)	77% (10/13)	NS
EDSS	4.2 ± 1.5	3.1 ± 1.7	.104
MSFC Z-score	.053 ± .27	.296 ± .54	.238

NS, not significant

EDSS, Expanded Disability Status Scale

MSFC, Multiple Sclerosis Functional Composite

Z-score, the degree to which MSFC results differed from those of a reference group (measured in standard deviations)

One placebo-treated participant did not complete all clinical assessments. One CYP-treated participant, a 61-year-old woman, died unexpectedly in her sleep. She had received a total dosage of 400 mg of CYP (two 200-mg doses) during the two weeks she had been in the study. No autopsy was performed, and her death was believed to be unrelated to treatment. The only

other serious adverse events—a cholecystectomy for cholecystitis and a benign breast mass—both occurred in a single CYP-treated participant. Mild adverse events that were observed in at least two patients are listed in Table 3. Macroscopic and microscopic hematuria unassociated with menstruation was not seen. More participants taking placebo (nine of 13) than CYP (three of 10) reported new weakness or stiffness and/or numbness or paresthesias without experiencing relapses ( $P = .10$ , Fisher's exact test, 2-tail). As expected, leukopenia and lymphopenia were significantly more frequent in the CYP group than in the placebo group. No patient experienced a significant change in menstruation during the period of the study.

**Table 3**  
**Number of patients with new adverse events that were not serious and occurred in more than one patient**

Adverse experience	Placebo	Cyclophosphamide
Hematologic		
Leukopenia	(< 1,800/mm <sup>3</sup> )	1 5
Monocytosis	5	5
Lymphopenia (< 400/mm <sup>3</sup> )	2	9
Anemia	1	3
Gastrointestinal		
Nausea/vomiting	8	6
Constipation	1	3
Diarrhea	2	2
Dyspepsia	1	2
Dysphagia	2	2
Abnormal liver function tests (excluding direct bilirubin)	2	2
Genitourinary		
Hesitancy	3	2
Urgency	3	3
Urinary tract infection	2	2
Menstrual irregularity	2	0
Diminished libido	0	2
Neuropsychiatric		
Insomnia	2	3
Headache	7	3
Depression	3	2
Confusion	1	1
Leg/low back pain	5	5
Arm pain	1	3
Abdominal/truncal pain	5	2
Dizziness	2	3
Paresthesias/numbness	5	1
Weakness/spasticity	7	2
Fatigue	3	2
Pulmonary		
Cough	2	1
Upper respiratory tract infection	5	4

No clinical outcome measure suggested that the combination of CYP and IFN $\beta$ -1a was associated with more progression of disease activity than IFN $\beta$ -1a alone (Table 4). The performance of three participants in the placebo group and none in the CYP group deteriorated for the Paced Auditory Serial Addition Test (PASAT)-3 by greater than 20%.

**Table 4**  
**Clinical outcome measures**

	Placebo – 13	Cyclophosphamide – 10
$\geq 20\%$ Worsening in $\geq 1$ subtest of MSFC*	5/12 (42%)	2/10 (20%)
Mean improvement in Z-score, comparing baseline #2 to month 9	.038 $\pm$ .290 (+ score improvement)	.102 $\pm$ .242 (+ score improvement)
Exacerbations	5	3
Sustained progression (3 months) <sup>†</sup>	4	2
Mean increase in EDSS, comparing baseline #2 to month 9	.61 $\pm$ .79	.10 $\pm$ .57

\* The major component in this difference was a 20% deterioration in the PASAT-3 for three placebo-treated patients that was sustained for three months.

<sup>†</sup> Defined as two consecutive EDSS scores 1 point above baseline for baseline scores of  $\leq 5.5$  and .5 point above baseline for scores of 6.0 or 6.5

MSFC, Multiple Sclerosis Functional Composite

Z-score, the degree to which MSFC results differed from those of a reference population's (measured in standard deviations)

EDSS, Expanded Disability Status Scale

Blinding was effective for the technician performing the MSFC testing, less effective for the patient, and ineffective for the physician (Table 5). The physician was unblinded by the occurrence of lymphopenia. Blinding of the participants may have been corrupted by their responses to treatment. Of the six patients who guessed that they had been treated with CYP, five felt better (actual treatment: four patients CYP and one patient placebo) and one felt unchanged (CYP).

**Table 5**  
**Blinding**

	Cyclophosphamide – 10			Placebo – 13		
	Correct	Unknown	Incorrect	Correct	Unknown	Incorrect
Patient	5	4	1	7	5	1
Technician	2	8	0	1	11	1
Physician	9	1	0	10	1	2

Four of 10 CYP-treated patients were able to maintain a maximal dosage of CYP. The average dose at the end of the study for all participants was 189  $\pm$  54 mg/m<sup>2</sup>, with all patients except one able to tolerate a dose of at least 150 mg/m<sup>2</sup>.

Few patients had measurable levels of cytokines intrinsically or in response to mitogen stimulation in preparations of their leukocytes. No pattern of alteration of cytokine levels was observed. All controls worked as expected.

## **CONCLUSION**

This study assessed the safety of the combination of oral CYP with IFN $\beta$ -1a administered over nine months for patients with clinically unstable MS while taking IFN $\beta$ -1a alone. Due to the small number of participants and the short duration of the study, it was impossible to form conclusions about the clinical benefit of this combination. Further, the examining physician was unblinded, the groups were imbalanced for disability, and baseline neutralizing antibody titers directed against IFN $\beta$ -1a were obtained for only some of the participants (seven participants had no detectable titers). Given these limitations, we found no evidence that the combination of CYP and IFN $\beta$ -1a produced a deterioration in clinical function. To the contrary, it appeared that the CYP-treated participants did slightly better than those taking IFN $\beta$ -1a alone.

The inability to demonstrate cytokine production in mitogen-stimulated PBLs was disappointing. It is unclear at this time whether the effect of the concomitant administration of IFN $\beta$ -1a, a technical problem in the way PBLs were handled, or a lack of assay sensitivity was responsible for this finding.

Side effects of treatment with the combination of oral CYP and IFN $\beta$ -1a were relatively few. Most participants easily tolerated 150 to 200 mg/m<sup>2</sup> of CYP given orally once a week. We have previously observed poor acceptance of intravenously administered cyclophosphamide and designed this trial to assess the tolerance of its oral administration among patients with active MS. The possibility of sterility was the most frequent reason given by subjects declining entry into this study. Cyclophosphamide is not likely to be an attractive treatment option when preservation of gonadal function is important to patients. The known long-term complications of CYP may deter its use. Cyclophosphamide can cause hemorrhagic cystitis and is mutagenic, inducing secondary leukemias, lymphomas, and bladder cancer.<sup>12</sup> Patients with non-Hodgkin's lymphoma treated with aggressive induction and salvage therapies and with oral cyclophosphamide, 100 mg/m<sup>2</sup> per day for 18 to 50 months, experienced seven times the expected incidence of transitional-cell carcinoma of the bladder (7/471) and exhibited a high occurrence of hemorrhagic cystitis (33/471).<sup>13</sup> This population also had an elevated risk of leukemia.<sup>14</sup> The authors of these reports cautioned against treatment of nonfatal diseases with maintenance cyclophosphamide. However, the weekly use of cyclophosphamide at one-quarter the monthly dose that was used to treat non-Hodgkin's lymphoma, as in this study, may greatly reduce its life-threatening effects. Since the utility of cyclophosphamide in the treatment of MS that is incompletely responsive to IFN $\beta$ -1a alone is not known, on the basis of this study, it may now be tested in combination with IFN $\beta$ -1a with few concerns about acute toxicity during nine months of treatment.

## **REFERENCES**

1. Jacobs LD, Cookfair DL, Rudick RA, et al. Intramuscular interferon beta-1a for disease progression in relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. *Ann Neurol*. 1996;39:285-294.
2. Simon JH, Jacobs LD, Campion M, et al. Magnetic resonance studies of intramuscular interferon b-1a for relapsing multiple sclerosis. The Multiple Sclerosis Collaborative Research Group. *Ann Neurol*. 1998;43:79-87.
3. Rudick RA, Goodkin DE, Jacobs LD, et al. Impact of interferon beta-1a on neurologic disability in relapsing multiple sclerosis. *Neurology*. 1997;49:358-363.

4. Hauser SL, Dawson DM, Leirich JR, et al. Intensive immunosuppression in progressive multiple sclerosis: a randomized, three-arm study of high-dose intravenous cyclophosphamide, plasma exchange, and ACTH. *N Engl J Med*. 1983;308:173-180.
5. Weiner HL, Mackin GA, Orav EJ, et al. Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: final report of the Northeast Cooperative Multiple Sclerosis Treatment Group. *Neurology*. 1993;43:910-918.
6. Canadian Cooperative Multiple Sclerosis Study Group. The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. *Lancet*. 1991;337:441-446.
7. Patti F, Cataldi ML, Nicoletti F, et al. Combination of cyclophosphamide and interferon-b halts progression in patients with rapidly transitional multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2001;71:404-407.
8. Weinstock-Guttman B, Kinkel RP, Cohen JA et al. Treatment of "transitional MS" with cyclophosphamide and methylprednisolone (CTX/MP) followed by interferon b. *Neurology*. 1997;48(suppl 2):A341 (Abstract).
9. Comabella M, Balashov K, Issazadeh S, et al. Elevated interleukin-12 in progressive multiple sclerosis correlates with disease activity and is normalized by pulse cyclophosphamide therapy. *J Clin Invest*. 1998;102:671-678.
10. Smith DR, Balashov KE, Hafler DA, et al. Immune deviation following pulse cyclophosphamide/methylprednisolone treatment of multiple sclerosis: increased interleukin-4 production and associated eosinophilia. *Ann Neurol*. 1997;42:313-318.
11. Fischer JS, Jak AJ, Kniker JE, et al. Administration and scoring manual for the multiple sclerosis functional composite measure (MSFC). New York: Demos; 1999.
12. CYTOXAN® (Cyclophosphamide) Product Information. Mead Johnson. In: Physician's Desk Reference®. 54th edition, Montvale, NJ: Medical Economics Company; 2000:859-861.
13. Pedersen-Bjergaard J, Ersboll J, Hansen VL, et al. Carcinoma of the urinary bladder after treatment with cyclophosphamide for non-Hodgkin's lymphoma. *N Engl J Med*. 1988;318:1028-1032.
14. Pedersen-Bjergaard J, Ersboll J, Sorensen HM, et al. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non-Hodgkin's lymphomas. *Ann Intern Med*. 1985;103:195-200.

## Influence of Infant Feeding Method on Postpartum Relapse of Mothers With MS

**Elsie E. Gulick, PhD, FAAN, and June Halper, ANP, FAAN**

Elsie E. Gulick is a Professor in the College of Nursing, Rutgers, The State University of New Jersey in Newark. June Halper is the Executive Director of the Bernard W. Gimbel Multiple Sclerosis Comprehensive Care Center at Holy Name Hospital in Teaneck, New Jersey.

### **Abstract**

*In an effort to determine relapse rates in breast-feeding and non-breast-feeding mothers with multiple sclerosis (MS) as well as differences in symptom prevalence between relapsing and non-relapsing mothers, weekly diaries through the first six postpartum months were kept by mothers to record the frequency and percentages of infant feeding by breast or formula and health problems that the mothers experienced. Of 140 mothers who breast-fed their infants, 35 (25%) experienced at least one neurologist-confirmed MS relapse during the first six months and 47 (33.6%) during the 12-month period; for non-breast-feeding mothers, 18 (51.4%) experienced relapse by six months and 22 (61.1%) by 12 months. MS relapse during pregnancy predicted increased relapse during the first three postpartum months while an increased percentage of infant feedings by breast predicted decreased relapse. Relapse the year before pregnancy and during pregnancy predicted increased relapse during the four- to six-month postpartum period. Length of time on immunomodulating therapy since delivery predicted increased relapse at seven to nine months. MS relapse during pregnancy predicted increased relapse at the 10- to 12-month period. For non-breast-feeding mothers none of the predictors of relapse were significant for the three-month period except use of immunomodulating therapy during the four- to six-month period when such use was associated with increased relapse. Relapsing compared with non-relapsing mothers reported significantly more MS-related symptoms during the three-month postpartum period. Decreased relapse rates during the first three months following delivery among breast-feeding mothers compared with non-breast-feeding mothers have implications for encouraging women with MS who wish to breast-feed their infants to do so, particularly if their pregnancy was free of relapse. Women with MS are also encouraged to postpone the initiation of immunomodulating therapy until three months following delivery or when breast-feeding is discontinued.*

Suggested Citation: Influence of Infant Feeding Method on Postpartum Relapse of Mothers with MS. Gullick, E. et al. *Int J MS Care*. (Serial on-line) 2002;4(4).

---

Few studies have been conducted regarding the effects of breast-feeding on relapse rates during the postpartum period among women with multiple sclerosis (MS), and those that have been conducted report dissimilar findings. Retrospective studies report relapse rates between .375 and .440 for breast-feeding and .305 and 1.00 for non-breast-feeding mothers during the first nine and 12 months postpartum.<sup>1,2</sup> In a prospective study consisting of four breast-feeding and four non-breast-feeding mothers, Birk et al<sup>3</sup> reported annualized relapse rates of 3.0 and 1.74 for the three- and six-month postpartum periods, respectively. Another prospective study reported relapse rates of 1.2 at three months and .9 at six months postpartum for breast-feeding mothers compared with 1.30 and 1.0 respectively for non-breast-feeding mothers.<sup>4</sup> These studies varied in sample size and, with the exception of one study,<sup>4</sup> failed to control for potential confounding factors that may influence relapse rates.

Unless potentially confounding influences on relapse rates are controlled, the true effects of breast-feeding on relapse rates cannot be discerned. The purpose of the current prospective study was to investigate further the effects of breast-feeding on relapse rates of mothers with MS who breast-fed their infants compared to those who did not, controlling for confounding factors before, during, and following the birth of their infants. Additionally, MS-related symptoms were examined between relapsing and non-relapsing mothers during the 12-month postpartum period.

## **METHODS**

### **Study Design and Recruitment of Subjects**

We used a prospective design to compare breast-feeding and non-breast-feeding mothers with MS on relapse rates and symptoms at one, three, six, nine, and 12 months postpartum. Mothers were recruited from the United States and Canada by Web site announcements through the Consortium of Multiple Sclerosis Centers/North American Research Committee (CMSC/NARCOMS), in newsletters of local chapters of the National Multiple Sclerosis Society (NMSS), and at MS outpatient clinics. The study was approved by Institutional Review Boards for Protection of Human Subjects among the recruitment agencies and the principal investigator's university. Included were women diagnosed with MS who had not yet delivered or whose infant was 1 month old or younger.

### **Procedure**

Women interested in participating in the study contacted the investigators by telephone or e-mail; other potential subjects were referred by staff members from MS outpatient clinics. Pregnant women (two thirds of the sample) were mailed consent forms that described elements of informed consent and were instructed to notify the principal investigator when delivery occurred, at which time the one-month study materials were sent. The signed consent form gave permission for the principal investigator to contact the subject's designated neurologist for confirmation of an MS relapse, should one occur. MS relapse was defined as the appearance or worsening of symptoms of neurologic dysfunction lasting more than 24 hours. Women who already had delivered (one third of the sample) were sent the consent form and the one-month study materials consisting of a Personal Data Inventory, MS-Related Symptom Scale, and three Health Diaries for the first three months postpartum. Self-addressed stamped envelopes were included for returning the completed material to the principal investigator. These study materials were sent to participants again at three, six, nine, and 12 months postpartum.

### **Sample**

Of 191 mothers who sought information about the study, 176 were enrolled. Of the 176 mothers, one was removed because she was subsequently diagnosed with Devic's disease. Of the 175 mothers, 140 (80%) breast-fed their infants for part or all of the 12-month period with an average of  $5.92 \pm 4.10$  months and 35 (20%) did not breast-feed. Of the non-breast-feeding mothers, 34 elected not to breast-feed and one mother, after an unsuccessful attempt for the first two days postpartum, decided to use total formula feedings. Breast-feeding mothers, on average, were about two years older, had one year more education, and experienced six months more duration of MS than did non-breast-feeding mothers (see Table 1). Of the breast-feeding mothers, 134 (95.7%) were married, compared with 31 (88.6%) non-breast-feeding mothers. The current birth represented the firstborn for 61 (43.6%) breast-feeding and 19 (54.3%) non-breast-feeding mothers. Most mothers in both groups were white (see Table 1) and had been classified with relapsing-remitting MS (see Table 2).

**Table 1**  
**Characteristics of 175 mothers with MS at birth of their infants**

Characteristic	Breast feeding mothers			Non-breast feeding mothers		
	N	%	Mean ±SD	N	%	Mean ± SD
Mean age	140	---	33.13 ± 4.05	35	---	30.74 ± 4.65
Education	140	---	15.55 ± 1.95	35	---	14.71 ± 2.31
MS duration	140	---	5.11 ± 4.09	35	---	4.43 ± 3.17
No. of children						
1	61	43.6	---	19	54.3	---
2	57	40.7	---	13	37.1	---
3 or more	22	15.7	---	3	8.6	---
Ethnicity						
White	132	94.3	---	34	97.1	---
Hispanic	4	2.9	---	---	---	---
Alaskan native	2	1.4	---	---	---	---
Black	1	.7	---	1	2.9	---
Asian	1	.7	---	---	---	---

**Table 2**  
**MS classification during pregnancy and year following birth**

MS Classification	Pregnancy		Six months postpartum		12 months postpartum	
	Breast N (%)	Non-breast N (%)	Breast N (%)	Non-breast N (%)	Breast N (%)	Non-breast N (%)
RR	128 (91.4)	31 (88.5)	128 (91.4)	30 (85.6)	126 (90.0)	28 (79.9)
PP	1 (.7)	---	1 (.7)	---	2 (1.4)	---
SP	5 (3.6)	1 (2.9)	5 (3.6)	1 (2.9)	6 (4.3)	3 (8.6)
PR	---	---	---	1 (2.9)	---	1 (2.9)
Missing *	6 (4.3)	3 (8.6)	6 (4.3)	3 (8.6)	6 (4.3)	3 (8.6)

\*Missing values were imputed as relapsing-remitting classification based on regression analysis  
RR, relapsing-remitting; PP, primary progressive; SP, secondary progressive; PR, progressive-relapsing

## Instruments

### Personal Data Inventory

The Personal Data Inventory sought information about the mother's age, educational level, age at MS diagnosis, marital status, number of children, ethnicity, and health status during pregnancy and delivery.

### MS-Related Symptom Scale (MS-RS)

The 26-item MS-RS consists of five factored subscales: motor, brainstem, sensory, mental/emotional, and elimination.<sup>5</sup> Respondents rated how frequently they experienced each symptom on a scale ranging from 0 (never) to 5 (always). Ratings were dichotomized as 1 (never or almost never) and 2 (occasionally to always). Satisfactory reliability and validity have been reported for the MS-RS.<sup>5-7</sup> Interrater agreement between the MS-RS subscales and Kurtzke Functional Systems ranged between 73% and 86%.<sup>6</sup> Reliability coefficients ranged between .51 and .91 for the subscales in the current study.

### Mother's Diary

Monthly diaries were used for the first six postpartum months to record weekly averages for percentage of feedings given each day by breast and/or formula. Prolactin levels are dependent upon the interval between sucking episodes and intensity.<sup>8,9</sup> Infant feeding by breast was coded as 0 (none), 1 (1% to 49%), 2 (50% to 79%), and 3 (80% to 100%) for each of the first six months. Codes assigned for breast-feeding at nine and 12 months were 0 (none) and 1 (some). Table 3 describes the percentage of infant feedings given by breast during the 12 postpartum months. The health diaries were also used to describe any health problems experienced by the mother that required telephone calls or office visits for medical care. At nine and 12 months, mothers were asked to indicate if immunomodulating drugs were being taken and, if so, which ones and when they were started. To evaluate the ongoing and cumulative effect of immunomodulating therapy, values for its use were calculated from the date following birth when therapy was initiated to the specific assessment month. For example, a mother who started therapy at 1.5 months following birth received a value of 1.5 at three months, 4.5 at six months, 7.5 at nine months, and 10.5 at 12 months. Mothers were also queried about health problems they may have experienced, and mothers who breast-fed their infants through six months were queried as to when they discontinued breast-feeding or if they were currently breast-feeding.

Information from mothers regarding relapse the year before pregnancy and their MS classification was sought at or shortly following the 12-month health assessment. Mothers who were uncertain about relapse the year before pregnancy or their MS classification gave permission for the first author to contact their neurologist.

### Analysis of Data

Descriptive statistics were used to describe study variables and inferential statistics to compare breast-feeding and non-breast-feeding groups on annualized relapse rates and MS symptoms. Due to missing data regarding MS relapse the year before pregnancy for six (4.3%) breast-feeding and three (8.6%) non-breast-feeding mothers, imputed values<sup>10</sup> were derived for missing data by regressing number of MS relapses the year before pregnancy on number of MS relapses during pregnancy, MS duration, and the age of the mother. Imputed values from nine of the mothers together with the available data were used in binary logistic regression to predict variables related to relapse rates during three-month postpartum period. Statistically significant results are reported at  $P < .05$  and are presented in Tables 1 through 6.

**Table 3**

**Percentage of infant feedings given by breast-feeding during the first six postpartum months and percentage of mothers continuing to breast-feed at nine and 12 months postpartum**

Month	N	None		1% to 49%		50% to 79%		80% to 100%	
		N	%	N	%	N	%	N	%
1	10*	7.1	8	5.7	10	7.1	112	80.0	
2	28	20.0	6	4.3	12	8.6	94	67.1	
3	46	32.9	9	6.4	7	5.0	78	55.7	
4	54	38.6	7	4.2	8	5.7	71	50.7	
5	65	46.4	7	5.0	9	6.4	59	42.1	
6	76	54.3	5	3.6	4	2.9	55	9.3	
Some breast-feeding									
9	40	28.6							
12	29	20.7							

\*These mothers breast-fed their infants for less than one month.

## RESULTS

### Percentage of Women Experiencing Relapse and Percentage Receiving Immunomodulating Therapy

Of 140 mothers who breast-fed their infants part or all of the first six postpartum months, 35 (25%) experienced one or more MS relapses compared with 18 (51.4%) of 35 non-breast-feeding mothers. During the 12-month postpartum period, 47 (33.6%) breast-feeding mothers experienced one or more MS relapses compared with 22 (62.9%) non-breast-feeding mothers. Average time to first relapse was significantly earlier among non-breast-feeding (3.12 months) compared with breast-feeding mothers (4.99 months). Of mothers who experienced relapse and began therapy during the 12-month postpartum period, 21.4% began therapy within two months of the relapse. About two thirds of non-breast-feeding mothers began taking one of the immunomodulating drugs by three months postpartum; this proportion increased to 80% by 12 months postpartum. In contrast, 16.4% of breast-feeding mothers were receiving immunomodulating drugs at three months, which increased to 53.6% by 12 months postpartum (see Table 4). For some mothers, anecdotal diary comments suggested that the presence of relapse influenced their decision to start immunomodulating therapy.

**Table 4**

**MS relapse and use of immunomodulating therapy**

Variable	Breast-feeding			Non-breast-feeding		
	N	%	Mean ± SD	N	%	Mean ± SD
≥ 1 MS relapse						
Zero to six months*	35	25	--	18	51.4	--
Zero to 12 months†	47	33.6	--	22	62.9	--
Time to 1st relapse(in months)‡	--	--	4.99 ± 3.43	--	--	3.12 ± 2.78
Received immuno-modulating Therapy						
0 to 3 months	23	16.4	--	28	65.7	--
4 to 6 months	50	35.7	--	26	74.3	--
7 to 9 months	66	47.1	--	27	77.1	--
10 to 12 months	75	53.6	--	28	80.0	--

Group differences: \* $\chi^2 = 9.263$ ,  $P = .002$ ; † $\chi^2 = 9.112$ ,  $P = .003$ ; ‡ $t = 2.200$ ,  $P = .031$

Seven (5%) mothers from the breast-feeding group received immunomodulating therapy concurrent with breast-feeding for an average of 6.6 months with a range between 3.7 and 11.1 months. Four of these mothers experienced a relapse shortly before starting therapy, two experienced a relapse after initiation of therapy and one mother experienced no relapse during the 12 postpartum months. Of the seven mothers, five received interferon (IFN) beta-1a therapy, one received glatiramer acetate, and one received IFN beta-1b therapy.

### Relapse Rates Without Control for Confounding Variables

Relapse rates for the two groups taking into account the number of relapses per mother, without control for potential confounding variables, were found to be significantly lower for the breast-feeding compared to non-breast-feeding mothers during the zero to three and seven to nine month postpartum periods (see Table 5). Although not statistically significant, lower relapse rates were also shown for breast-feeding compared to non-breast-feeding mothers during four to six and 10 to 12 postpartum months. Relapse rates during the pregnancy period were higher for non-breast-feeding compared to breast-feeding mothers and approached being statistically significant. Relapse rates during the year preceding the pregnancy period were similar for both groups of mothers (see Table 5).

**Table 5**  
**Relapse rate of mothers with MS in relation to whether or not they breast-fed their infants**

Period	Breastfeeding		Non-breast-feeding		Mann-Whitney U Test	
	No. of relapse	Relapse rate	No. of relapse	Relapse rate	Z score	P value
Yr. before preg.	81	.58	20	.57	.124	.902
Pregnancy	15	.14	9	.34	1.956	.051
Yr. after preg.						
Months 0 to 3	17	.49	15	1.71	4.192	< .001
Months 4 to 6	19	.54	9	1.03	1.748	.081
Months 7 to 9	10	.29	7	.82	2.362	.018
Months 10 to 12	13	.37	4	.47	.435	.663

### Relapse Rates Controlling for Confounding Variables

Binary logistic regression was used to determine predictors of none versus one or more relapses for zero to three, four to six, seven to nine, and 10-12 month postpartum periods separately for breast-feeding and non-breast-feeding groups. There was controlling for potentially confounding variables pertaining to number of relapses the year before pregnancy, number of relapses during pregnancy, age of mother at delivery, duration of MS since diagnosis, educational level, and use of immunomodulating therapy. The variables relative to mother's age at delivery, MS duration, and educational level failed to emerge as significant predictors of relapse at any of the postpartum periods.

Breast-feeding mothers who experienced MS relapse during pregnancy were six times more likely to experience MS relapse during the first three months postpartum than were mothers who did not experience a relapse during pregnancy. However, after controlling for the effects of MS relapse during pregnancy, the mothers who gave the majority of infant feedings by breast during the first three months postpartum experienced 63% fewer MS relapses than those mothers who stopped or markedly reduced the percent of infant feedings by breast (see Table 6 for statistical results).

**Table 6**  
**Logistic regression used to predict MS relapse during the postpartum**

Postpartum months	Predictor variable	Beta	P value	Odds ratio	95% Confidence interval
Breast-feeding mothers (n = 140)					
0-3	Relapse during pregnancy	1.91	.011	6.75	1.54 - 29.65
0-3	% of breast-feeding	.46	0.35	.63	41 - 97
4-6	Relapse year before pregnancy	.78	.014	2.19	1.17 - 4.08
4-6	Relapse during pregnancy	1.11	.042	3.02	1.04 - 8.77
7-9	Immunomodulating therapy	.32	.023	1.37	1.05 - 1.80
10-12	Relapse during pregnancy	1.01	0.49	2.76	1.00 - 7.57
Non-breast-feeding mothers (n=35)					
4-6	Immunomodulating therapy	.51	-.47	1.66	1.01 - 2.73

During the four to six month postpartum period, mothers in the breast-feeding group who experienced relapse the year before and during pregnancy were two and three times, respectively, more likely to experience relapse during the four to six months postpartum than those who did not experience such relapses. Breast-feeding did not emerge as having a significant effect on MS relapse rate during the four to six months postpartum after controlling for the confounding variables (see Table 6 for statistical results).

During the seven to nine month postpartum period, mothers in the breast-feeding group who began immunomodulating therapy were one and one third times more likely to experience relapse during this period than those who did not receive immunomodulating therapy. Breast-feeding did not emerge as having a significant effect on MS relapse rate during the seven to nine months postpartum after controlling for the confounding variables (see Table 6 for statistical results).

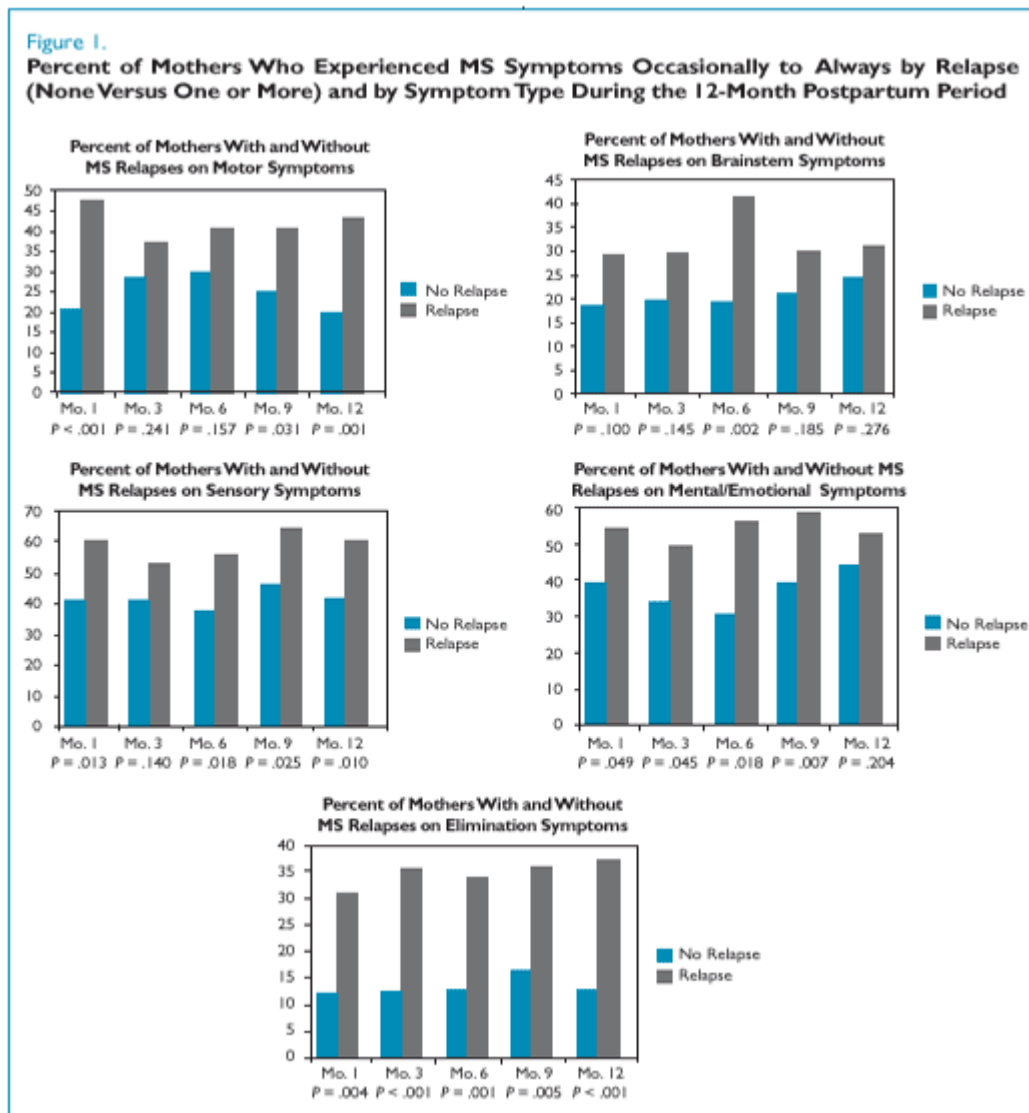
During the 10 to 12 month postpartum period, mothers in the breast-feeding group who experienced MS relapse during pregnancy were twice as likely to experience relapse during the 10 to 12 month period than those who did not experience relapse during pregnancy. Again, breast-feeding did not emerge as having a significant effect on MS relapse rate during 10 to 12 months postpartum after controlling for the confounding variables (see Table 6 for statistical results).

For non-breast-feeding mothers, only the confounding variables were examined at zero to three, four to six, seven to nine, and 10 to 12 month postpartum periods. None of the confounding variables including number of relapses the year before pregnancy, number of relapses during pregnancy, age of mother at delivery, duration of MS since diagnosis, educational level, and use of immunomodulating therapy were significant predictors of MS relapse during the zero to three, seven to nine, and 10 to 12 month postpartum periods.

However, use of immunomodulating therapy was a significant predictor of relapse during the four to six month period. Mothers who used immunomodulating therapy were 1.66 times more likely to have experienced relapse during this period than mothers who did not experience relapse (see Table 6 for statistical results).

### Symptoms During MS Relapses

Not unexpectedly, mothers who experienced MS relapse reported more symptoms than mothers who did not experience a relapse. Significantly more motor symptoms were reported by relapsing mothers at one, nine, and 12 months postpartum; more brainstem at six months; more sensory at one, six, nine, and 12 months; more mental/emotional at one, three, six, and nine months; and more elimination symptoms at one, three, six, nine, and 12 months (see Figure 1). The prevalent symptom among the groups was sensory symptoms followed by mental/emotional, motor, brainstem, and elimination.



## **DISCUSSION**

MS relapse rates found in the current study for non-breast-feeding compared with breast-feeding mothers were more than triple for the one to three postpartum months, about double for the four to six postpartum months, and nearly triple for the seven to nine postpartum months. However, little difference was observed between these two groups during the 10 to 12 postpartum months, which reflected rates relatively similar to those of the year before pregnancy. Relapse rates during pregnancy, although low and not statistically significant, were higher among non-breast-feeding than breast-feeding mothers.

Relapse rates the year before and during pregnancy found in the current study for breast-feeding and non-breast-feeding mothers were relatively similar to those reported by Confavreux et al.<sup>4</sup> In contrast, relapse rates were less than one half the rate reported by Confavreux et al.<sup>4</sup> during the first three postpartum months, about half at four to six months, less than half at seven to nine months, and slightly less at 10 to 12 months. Of particular import is the finding in the current study that breast-feeding compared to non-breast-feeding mothers had statistically significantly fewer relapses during the zero- to three-month period after controlling for the effects of relapse the year before and during pregnancy, age of mother, duration of MS, educational level and use of immunomodulating therapy. These findings are in contrast to Confavreux et al.<sup>4</sup> who did not find significant differences between relapse among breast-feeding and non-breast-feeding groups for any of the three-month postpartum periods despite adjustment for the mother's age, duration of MS, and occurrence of relapse one year before and during pregnancy. However, Confavreux et al.<sup>4</sup> did find significantly fewer relapses among breast-feeding mothers when relapses during the year before pregnancy, pregnancy period, and year following pregnancy were combined.

Breast-feeding mothers reported one third the relapse rate of non-breast-feeding mothers at three months postpartum, a rate comparable to the yearly rate reported by persons with MS who receive one of the immunomodulating therapies: IFN beta-1b, glatiramer acetate, and IFN beta-1a.<sup>11</sup> During the first six and 12 postpartum months the relapse rate for breast-feeding mothers was less than one fifth and one half, respectively, that of non-breast-feeding mothers.

It is unclear why some mothers who were receiving immunomodulating therapy during the postpartum period experienced more relapses than mothers who were not receiving such therapy. One reason might be incomplete protection as a result of medication titration, a procedure frequently used when initiating therapy aimed at minimizing drug adverse effects.<sup>12</sup> Another reason might be the immunosuppressant drug used being less effective than another one, or possibly a need for combining therapies.<sup>13</sup>

Although not statistically significant, proportionately more non-breast-feeding mothers ( $n = 7$ , 20%) compared to breast-feeding mothers ( $n = 12$ , 8.6%) reported experiencing MS relapse during their pregnancy. Experiencing a relapse during pregnancy may be a deterrent to breast-feeding and a possible reason for initiating or resuming immunomodulating therapy soon after giving birth. However, of the seven non-breast-feeding mothers who experienced relapse during their pregnancy, only four were receiving immunomodulating therapy by three months postpartum. This suggests that factors other than immunomodulating therapy influence the mother's decision to forego breast-feeding.

One explanation for fewer relapses experienced by breast-feeding compared to non-breast-feeding mothers may be increased circulating levels of prolactin, which has immunomodulating capabilities.<sup>14</sup> Prolactin levels in fully breast-feeding mothers are triple those of non-breast-feeding mothers during the first 12 to 20 postpartum weeks and then gradually decline.<sup>8</sup> The decline in prolactin level is hastened when infant sucking at the breast is diminished by supplementation with artificial milk and/or other foods.<sup>8,9</sup> In central Africa, where breast-feeding is sustained for two years and mothers give the breast more than six times per day,

serum prolactin levels did not decline significantly during the first postpartum year.<sup>15</sup> The immunosuppressant effect of increased levels of prolactin may be due in part to a decreased natural killer cell activity in the presence of hyperprolactinemia.<sup>14,16</sup>

Another explanation for the fewer relapses experienced by breast-feeding compared to non-breast-feeding mothers may be the immune suppression resulting from an increased level of serum cortisol that accompanies breast-feeding due to the infant sucking that stimulates release of ACTH and subsequent increase in cortisol production.<sup>17</sup> Corticosterones inhibit antigen-induced T cell proliferation by macrophages.<sup>18</sup>

Retrospective<sup>1,19,20</sup> and prospective studies<sup>3,4,21-22</sup> indicate that fewer relapses occur during the pregnancy period, but they increase two to three times during the three to six month postpartum period compared to nonpregnant and nonpostpartum periods. Both prolactin<sup>23</sup> and cortisol<sup>24</sup> levels increase significantly during the pregnancy period and may contribute to the apparent immune suppression that is evidenced in pregnant women with MS.

Research is needed to investigate the role that elevated prolactin and cortisol levels may have on MS relapse rates of mothers who breast-feed their infants. These hormones may have immune modulating action in which decreases in CD4+ killer and increases in CD8+ suppressor T cells or related cytokines occur.

The prevalence of motor, brainstem, and mental/emotional symptoms found in the current study for nonrelapsing mothers is similar to that commonly experienced during relapsing-remitting MS<sup>25</sup> but is much higher for the relapsing mothers. However, the prevalence of sensory and elimination symptoms among nonrelapsing mothers in the current study was higher by approximately double and triple, respectively, than reported by Whitney.<sup>25</sup> The increased prevalence of elimination symptoms may have been associated with weakened pelvic floor muscles due to childbirth, making this area vulnerable to incontinence during MS relapse.

Perhaps the most serious challenge to these data concerns the possibility that some mothers may not have had definite MS. However, MS relapses reported by the mothers were confirmed by their attending neurologists. Further, the mothers' reports of symptoms are consistent with MS and MS relapse.

## **CONCLUSION**

Decreased relapse rates during the first three months following birth among breast-feeding mothers, after controlling for mother's age, MS duration, educational level, use of immunomodulating drugs, and relapses the year before and during pregnancy, compared to non-breast-feeding mothers has implications for encouraging women with MS who wish to breast-feed their infants to do so, particularly if their pregnancy was free of relapse, and to postpone the initiation of immunomodulating therapy until after three months or when breast-feeding is discontinued. Although the study findings cannot conclude that breast-feeding causes decreased relapse rates during the postpartum period, the significant association between increased breast-feeding and decreased postpartum MS relapse warrants further study. Studies are needed to determine prolactin and cortisol levels in breast-feeding mothers together with levels of CD4+ and CD8+ T cells and related cytokines to determine if they are associated with postpartum relapse.

---

**REFERENCES**

1. Nelson LM, Franklin GM, Jones MC. Risk of multiple sclerosis exacerbation during pregnancy and breast-feeding. *JAMA*. 1988;259:3441-3443.
2. Gulick EE, Halper J, Picone M. Health of mothers with multiple sclerosis during the first year following birth. *Consort*. 1996;7:7.
3. Birk K, Ford C, Smeltzer S, et al. The clinical course of multiple sclerosis during pregnancy and the puerperium. *Arch Neurol*. 1990;47:738-742.
4. Confavreux C, Hutchinson M, Hours MM, et al. Rate of pregnancy-related relapse in multiple sclerosis. *N Engl J Med*. 1998;339:285-291.
5. Gulick EE. Model confirmation of the MS-Related Symptom Checklist. *Nurs Res*. 1980;38:147-153.
6. Gulick EE, Cook SD, Troiano R. Comparison of patient and staff assessment of MS patients' health status. *Acta Neurol Scand*. 1993;88:87-93.
7. Gulick EE. Correlates of quality of life among persons with multiple sclerosis. *Nurs Res*. 1997;46:305-311.
8. Glasier A, McNeilly AS, Howie PW. The prolactin response to suckling. *Clin Endocrinol*. 1984;21:109-116.
9. Howie PW, McNeilly AS, Houston MJ, et al. Fertility after childbirth: infant feeding patterns, basal PRL levels and post-partum ovulation. *Clin Endocrinol*. 1982;17:315-322.
10. Rubin DB. Multiple Imputation for Nonresponse in Surveys. New York, NY: John Wiley & Sons; 1987.
11. Miller A, Johnson KP, Murray TJ, et al. Disease-modifying therapies: an update. *MS Grand Rounds*. 2002;4:2-15.
12. Denis L, Gagnon N, Lowden, et al. New therapies. In Halper J, ed. *Advanced Concepts in Multiple Sclerosis Nursing Care*. New York, NY: Demos; 1985:149-173.
13. Kaufman M. Combining therapies with interferon beta for relapsing and early progressive MS: a review. *Int J MS Care*. 2002;4:50-51,56-60,63-65.
14. Reber PM. Prolactin and immunomodulation. *Am J Med*. 1993;95:637-644.
15. Delvoeye P, Demaegd M, Delogne-Desnoeck J. The influence of the frequency of nursing and of previous lactation experience on serum prolactin in lactating mothers. *J Biosoc Sci*. 1977;9:447-451.
16. Gerli R, Rambotti P, Nicoletti I, et al. Reduced number of natural killer cells in patients with pathological hyperprolactinemia. *Clin Exp Immunol*. 1986;64:399-406.
17. Mepham TB. *Physiology of Lactation*. Philadelphia, Pa: Open University Press; 1987.
18. Snyder DS, Unanue ER. Corticosteroids inhibit murine macrophage Ia expression and interleukin 1 production. *J Immunol*. 1982;129:1803-1805.
19. Korn-Lubetzki I, Kahana E, Cooper G, Abramsky O. Activity of multiple sclerosis during pregnancy and puerperium. *Ann Neurol*. 1984;16:229-231.
20. Frith JA, McLeod JG. Pregnancy and multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1988;51:495-498.
21. Sadovnick AD, Eisen K, Hashimoto A, et al. Pregnancy and multiple sclerosis. *Arch Neurol*. 1994;51:1120-1124.
22. Worthington J, Jones R, Crawford M, Forti A. Pregnancy and multiple sclerosis—a 3-year prospective study. *J Neurol*. 1994;241:228-233.
23. Tyson JE, Hwang P, Guyda H, Friesen HG. Studies of prolactin secretion in human pregnancy. *Am J Obstet Gynecol*. 1972;113:14-20.
24. Meulenberg PMM, Hofman JA. Differences between concentrations of salivary cortisol and cortisone and free cortisol and cortisone in plasma during pregnancy and postpartum. *Clin Chem*. 1990;36:70-75.
25. Whitney DK. Early diagnosis and intervention in multiple sclerosis. *Int J MS Care*. 2001;3:8-14.