

THERAPY AFTER ACUTE CERVICAL SPINAL CORD INJURY

RECOMMENDATIONS

Corticosteroids:

- Standards:** There is insufficient evidence to support treatment standards.
- Guidelines:** There is insufficient evidence to support treatment guidelines.
- Options:** Treatment with There is insufficient evidence to support treatment standards. Methylprednisolone for either 24 or 48 hours is recommended as an option in the treatment of patients with acute spinal cord injuries that should be undertaken only with the knowledge that the evidence suggesting harmful side effects is more consistent than any suggestion of clinical benefit.

GM-1 Ganglioside:

- Standards:** There is insufficient evidence to support treatment standards.
- Guidelines:** There is insufficient evidence to support treatment guidelines.
- Options:** Treatment of patients with acute spinal cord injuries with GM-1 ganglioside is recommended as an option without demonstrated clinical benefit.

RATIONALE

The hope that administration of a pharmacological agent delivered shortly after acute spinal cord injury (ASCI) might improve neurological function and/or assist neurological recovery has long been held. A variety of promising substances have been tested in animal models of ASCI, but few have had potential application to human spinal cord injury (SCI) patients. Four pharmacological substances have met rigorous criteria in laboratory testing and initial human investigations: two corticosteroids (methylprednisolone and tirilazad mesylate), naloxone, and GM-1 ganglioside. All four pharmacological agents have been evaluated in controlled, randomized, blinded clinical trials of human patients with ASCIs. Two of these substances, tirilazad and naloxone, have been studied less extensively and as yet have unclear efficacy in the management of acute human SCI. The purpose of this medical evidence-based review is to define the usefulness of administration of methylprednisolone with or without GM-1 ganglioside in the contemporary management of ASCI patients.

SEARCH CRITERIA

A computerized search of the National Library of Medicine database of literature published from 1966 to 2001 was undertaken. The following medical subject headings were used in combination with "spinal cord injury" and "neurological deficit": steroids, methylprednisolone, and GM-1 ganglioside. Approximately 2400 citations were acquired. Non-English language citations and nonhuman experimental studies were deleted. Titles and abstracts of 652 manuscripts were reviewed, 639 on the topic of corticosteroids and human SCI and 13 on the topic of GM-1 ganglioside and human SCI. Additional references were culled from the reference lists of the remaining papers. Finally, the members of the author group were asked to contribute articles known to them on the subject matter that were not found by other search means. Duplications, case reports, pharmacokinetic reports, general reviews, and articles with mention of one agent or another but without scientific assessment were eliminated. Several editorials, critiques, and responses to published reports and studies were included. Forty-six published references on the topic of methylprednisolone in the treatment of patients with ASCI and seven published

references for GM-1 ganglioside provide the basis for this guideline. Thirteen studies on methylprednisolone and two studies on GM-1 ganglioside are summarized in Tables 9.1 and 9.2.

SCIENTIFIC FOUNDATION

Methylprednisolone

Corticosteroids, particularly methylprednisolone, have been studied extensively in animal models of SCI (2,19,47,48,50,51). Although their precise mechanisms of action are not completely known, they have the potential to stabilize membrane structures, maintain the blood-spinal cord barrier potentially reducing vasogenic edema, enhance spinal cord blood flow, alter electrolyte concentrations at the site of injury, inhibit endorphin release, scavenge damaging free radicals, and limit the inflammatory response after injury (2,47,48,50,51). After considerable positive study in the laboratory, methylprednisolone was studied in human SCI patients in a multicenter, randomized, double-blinded clinical trial initiated in 1979. The first National Acute Spinal Cord Injury Study (NASCIS I) (11), reported in 1984, compared the efficacy of administration of a 100-mg bolus of methylprednisolone and then 100 mg daily thereafter for 10 days with administration of a 1000-mg bolus and then 1000 mg daily for 10 days in 330 acute injury patients assessed 6 weeks and 6 months after injury. There was no control group. The study revealed no difference in neurological recovery (motor or sensory function) between the treatment groups at either 6 weeks or 6 months after injury. Motor scores were determined from the examination of seven muscle groups on each side of the body scored on a 6-point scale. Sensory function was assessed using a 3-point scale of dermatomal light touch and pinprick sensation. The authors reported the motor and sensory scores from the right side of the body only. There was no anatomic level injury limit (superior to T12 vertebral level, for example) in the study to include only SCI patients and exclude primary cauda equina injuries or “mixed” central and cauda equina injuries that might occur with a lower fracture injury (e.g., T12-L1 or L1-L2 injuries). The study did not require a minimum motor impairment for inclusion; hence, patients with normal motor examinations and those with minimal neurological deficits were included in the study if the attending physician determined that the patient had an SCI of any severity. In 1985, the same group of investigators reported on the 1-year follow-up of these study patients (15). No differences in motor or sensory outcome were identified between the two treatment groups.

Animal studies of the efficacy of methylprednisolone after experimental SCI suggested that the doses of methylprednisolone used in the NASCIS I investigation were too low to demonstrate a significant in outcome (2,14,19,50,51). A multicenter NASCIS II trial was initiated in 1985 using a much higher dose of methylprednisolone (30 mg/kg as a bolus and then 5.4 mg/kg/h infusion for 23 h). These patients were compared with similarly injured patients who received either naloxone (5.4 mg/kg bolus and then an infusion of 4.0 mg/kg/h for 23 h) or placebo. Patients had to be randomized to one of three treatment arms within 12 hours of ASCI. The results of NASCIS II were reported in 1990 (14). Four hundred eighty-seven patients were entered into the study; 162 received methylprednisolone, 154 were given naloxone, and 171 patients were in the placebo control group. The authors reported that the administration of methylprednisolone within 8 hours of injury was associated with a significant improvement in motor function (neurological change scores, right side of body only, $P = 0.03$), and in sensation (pinprick, $P = 0.02$; light touch, $P=0.03$) at the 6-month follow-up compared with patients receiving methylprednisolone more than 8 hours after injury and patients receiving naloxone or placebo. No similar significant improvements were noted at the 6-week follow-up, either motor or sensory. Motor scores were determined from the examination of seven muscle groups on each side of the body scored on a scale of 0 to 5 points. Sensory function was assessed using a 3-point scale of dermatomal light touch and pinprick sensation. The NASCIS II study reported on the motor scores from the right side of the body only. Bilateral sensory scores were provided. Like the NASCIS I study, there was no anatomic level injury limit in the study (superior to T12 vertebral level, for example) to ensure that only SCI

patients were included for study (11,15). Similarly, NASCIS II did not require a minimum motor impairment for inclusion; hence, patients with normal motor examinations and those with minimal neurological deficits were included. No outcome measures involving patient function were used in this study. In 1992, NASCIS investigators reported on the 1-year follow-up of NASCIS II study patients (13). They reported statistically significant improvement in motor scores on the right side of the body for 62 of 487 study patients ($P = 0.03$). These 62 patients received methylprednisolone within 8 hours of injury. Significant right body motor score improvement was identified in two of three categories of patients, plegic patients with total sensory loss ($P = 0.019$) and paretic patients with variable sensory loss ($P = 0.024$), but not among plegic patients with partial sensory loss ($P = 0.481$). There were no significant improvements in motor change scores described among the remaining 421 patients entered in the study. There were no significant differences in sensory scores for any treatment group or categories of patients despite the differences reported at the 6-month follow-up for patients receiving methylprednisolone within 8 hours of injury. Patients treated more than 8 hours after injury with methylprednisolone or naloxone experienced less recovery of motor function compared with placebo treatment patients. The authors concluded that treatment with the study dose of methylprednisolone administered within 8 hours of injury improves neurological outcome and is therefore indicated in the treatment of patients with ASCI. The use of study dose methylprednisolone in patients was not associated with harmful side effects compared with patients in the other treatment groups, although the authors reported an increased incidence of wound infection and gastrointestinal bleeding among corticosteroid-treated patients. Treatment with methylprednisolone beyond 8 hours after injury was not recommended.

There are several flaws in the NASCIS II study, and criticism has been offered on several methodological, scientific, and statistical issues (18,19,22,31,32,35,37,40-42,44-46,51). The investigators described two a priori hypotheses: that treatment effect would be influenced by how soon the drug was given after injury and by the severity of injury. Patients were considered eligible for inclusion if they were admitted to the study and randomized to treatment within 12 hours of injury. At some point, patient outcome was stratified according to the timing of methylprednisolone administration (<8h, >8h). Some reviewers have requested examination of the raw data to look for time-related diminishing effects of methylprednisolone administration relative to injury rather than assignment of an "all or nothing" time cutoff (18,32,37,40,42,51). Analysis of results of the entire population of patients according to the second a priori hypothesis was not provided by the authors (18,31,37,40,42,51). Analysis using the second hypothesis was accomplished on the group of patients previously stratified according to the first hypothesis. It may be that the two hypotheses are fully independent, yet no justification for this assumption was offered (31,40). The study did not offer a standardized medical treatment regimen for all ASCI patients in this study. The medical management of study patients including monitoring, blood pressure augmentation, respiratory care, deep venous thrombosis prophylaxis, nutritional support, and initiation of rehabilitation activities was neither consistent within centers nor consistent from center to center (18,22,31,37). Similarly, surgical treatment offered to patients in the NASCIS II study was not consistent from center to center (19,31,35,51). There was no description of surgical approaches used for specific pathology or documentation of the timing of surgical intervention for individual patients. There was no consideration given to the independent effect that either aggressive medical management or surgery had, or may have had, on outcome (18,19,22,31,35,37,51).

The most important and significant criticism of the NASCIS II study is the failure to measure patient functional recovery (e.g. functional independence measure [FIM]) to determine animation (change in motor scores) in the methylprednisolone treated patients had meaningful clinical significance (18,32,35,37,44). It is unclear from the change in score data provided whether the improvement had any clinical significance to the injured patients (1,18,32,35,37,44-46). One of the most frequent criticisms of the reported NASCIS II results is the failure to provide scientific data on which statistical comparisons were made (18,19,31,32,37,40-42,46,51). As with the NASCIS I study, only right-sided motor scores were reported in NASCIS II, but bilateral sensory scores were reported. Change in motor score

(improvement) on the right side only of ASCI patients has been cited by the study authors as a significant neurological benefit associated with methylprednisolone administration given at study doses within 8 hours of injury and assessed at 6-month and 1-year follow-up ($P = 0.03$) (13,14). These findings were observed in only a small subset of study patients (18,31,37,41). Was this an a priori hypothesis of the investigators and was the result significant for the whole population of patients? If so, then the finding stands and the post hoc subgroup analysis suggests which subgroup receives the benefit. If, however, the entire result is from a post hoc hypothesis and analysis and is significant only for the subgroup and not for all of the patients analyzed together, then it is a weak suggestive finding. This is not made clear by the authors. Reviewers have argued against the use of right-side only motor scores, and particularly the change of score results in NASCIS II publications (18,22,31,32,40,41). The lack of evidence describing left-sided motor scores and total body motor scores in NASCIS II is confusing (4,8-10,12,50).

Also confusing is the reported difference in change of motor score outcome for patients with incomplete SCI who were in the placebo treatment arm. Patients with incomplete SCIs in the NASCIS II study who received placebo more than 8 hours after injury had significantly better neurological recovery than did patients who received placebo within 8 hours of injury (13,18,32,42). Additionally, the neurological recovery curve generated for patients with incomplete SCIs treated with methylprednisolone within 8 hours of injury is virtually identical to that of patients with incomplete SCIs treated with placebo beyond 8 hours after injury. The benefit of treatment with respect to neurological recovery (motor change score) with methylprednisolone given within 8 hours of injury seems equal to treatment with placebo more than 8 hours after injury (18,37,42).

Statistical criticisms of the NASCIS II results are many (18,19,22,31,32,40-42,45,46,51). They include potential interpretive errors, problematic statistical comparisons, simplification of subgroup analysis from the pre-planned 15 categories to 3 seemingly arbitrarily determined categories, an improper and incomplete presentation of odds ratios, and a post hoc analysis of study data including only 127 patients (62 methylprednisolone, 65 placebo) treated within 8 hours of injury, rather than the entire study population of 487 patients (18,19,22,31,32,40-42,45,46,51). NASCIS II was designed and implemented to be a randomized, controlled, double-blinded clinical study in an attempt to generate Class I evidence on the efficacy of methylprednisolone and naloxone after ASCI in human subjects. The lack of a measure of functional significance, the dependence on post hoc analyses, and the absence of an analysis of surgical treatment diminish the quality and usefulness of the evidence provided by these studies.

In 1993, Galandiuk et al (21) described 32 patients with cervical or upper thoracic ASCIs managed in an urban trauma center. Fourteen patients who received NASCIS II doses of methylprednisolone within 8 hours of injury were compared with 18 ASCI patients with similar injuries managed without corticosteroids. The authors reported no difference in neurological outcome between the two sets of patients but noted that methylprednisolone-treated patients had immune response alterations (lower percentage and density of monocyte Class II antigen expression and lower T-cell helper/suppressor cell ratios), a higher rate of pneumonia (79% versus 50%), and longer hospital stays (44.4 d versus 27.7 d) than similar ASCI patients they managed without administration of corticosteroids. Although the conclusions drawn by the authors are interesting, they have little scientific power. The mix of historical patients with contemporary patients, the lack of a prospective design, and the haphazard assignment and assessment of patients dilute the quality of the evidence provided.

Bracken and Holford (8) described the effect of timing of methylprednisolone on neurological recover in NASCIS II study patients in 1993. They concluded from post hoc analysis of the NASCIS II data that methylprednisolone administered to patients within 8 hours of ASCI improves neurological function below the level of the spinal cord lesion in patients initially diagnosed as having complete or incomplete injuries. The majority of the improvements they reported were among patients with incomplete SCIs at admission. Complete injury patients demonstrated very little recovery below the level

of injury irrespective of treatment. Their post hoc analysis also confirmed that methylprednisolone administered more than 8 hours after injury may be associated with a worse neurological outcome.

This 1993 article (8) refers to and references the 1-year follow-up NASCIS II study data, but only describes patient groups and offers percentages (18,42). It provides neither new evidence nor the numbers of patients on whom Bracken and Holford based their conclusions. Although the result that the authors describe is positive (methylprednisolone administered within 8 h of injury improves spinal cord function in patients with SCI), it was identified in a very small subgroup of patients, which raises questions as to its true weight and validity. The manner in which the data and conclusions were presented is ambiguous and suggests that this was a positive result reflected by analysis of the entire NASCIS II study population ($n = 487$) (18). In fact, it was only a subgroup analysis of the population of patients who received methylprednisolone within 8 hours of injury ($n = 62$), compared with those who received placebo within 8 hours of injury ($n = 65$). Forty-five methylprednisolone-treated patients had complete injuries and demonstrated very little change in function below the level of injury. The same is true for 43 similar (complete) patients who received placebo (no significant difference). The actual differences described by the authors are based on 17 methylprednisolone patients compared with 22 placebo-treated patients, all of whom had incomplete SCI and had therapy initiated within 8 hours of injury (18).

Their report (8) does help to clarify the issue of recovery of function (motor score change) in NASCIS II patients with complete injuries at admission who received methylprednisolone within 8 hours of injury. The NASCIS II results at 1 year cite a significant improvement in motor function for patients who received methylprednisolone at study doses within 8 hours of injury compared with placebo-treated patients ($P=0.03$) (13). For the patients who had complete injuries who met the early treatment criteria ($n=45$), the significance of improvement (change in motor score) was $P = 0.019$, compared with similar patients who received placebo. Bracken and Holford's (8) post hoc analysis revealed no significant difference in recovery below the level of the lesion in these patients compared with placebo-treated patients. This suggests that the primary improvements in function identified in the NASCIS II study for patients with complete spinal injuries treated within 8 hours were at the level of injury, likely root recovery, rather than a significant gain in spinal cord function (18). Again, the relationship between any such recovery and an improvement in patient function is unknown, irrespective of the sample size, because the study did not use functional outcome assessments (18,35,37).

In 1994, Duh et al (20) reported on the effect of surgery on outcome among NASCIS II study patients. In all, 298 of 487 study patients underwent 303 operative procedures, 56 via the anterior approach and 247 via the posterior approach. The authors examined the influence of surgery on neurological outcome across all study groups of patients at time periods of less than 25 hours, 26 to 50 hours, 51 to 100 hours, 101 to 200 hours, and more than 200 hours. They found that the most severely injured patients were less likely to be treated surgically. The authors did not identify significant differences in outcome, motor or sensory, with surgical treatment, either early or late. Functional recovery was not measured.

Gerhart et al (29), in 1995, reported a population-based, concurrent cohort comparison study of 363 ASCI survivors treated in Colorado. Two hundred eighteen patients were managed between May 1990 and December 1991, and 145 injury patients were managed 2 years later in 1993. Of 218 patients managed in 1990 to 1991, 100 (46%) were treated according to the NASCIS II protocol. Fifty-one patients (23%) received no methylprednisolone, and 67 patients (31%) received another corticosteroids, were given an incorrect dose, or had insufficient data. In the 1993 study population, 61% of ASCI patients ($n = 88$) received methylprednisolone according to NASCIS II protocol. Thirty-nine patients (27%) received no methylprednisolone and 18 patients (13%) were given another corticosteroid, received an incorrect dose, or had insufficient data. The authors reported no significant differences in outcome as

assessed by the Frankel scale at the time of hospital discharge when 188 patients who received protocol methylprednisolone (appropriate dose and timing) were compared with those ($n = 90$) who did not receive any methylprednisolone during treatment. This was true for the combined population of patients and for both the 1990 to 1991 and the 1993 patient populations. It does not seem, however, that adequate numbers of patients were analyzed by the authors, substantially diluting the statistical power of their findings.

In 1995, George et al (28) reported their experience with ASCI patients at Michigan State University from 1989 through 1992. One hundred forty-five patients were described, 80 of whom were treated with methylprednisolone per the NASCIS II protocol (MP group) and 65 of whom did not receive methylprednisolone (No-MP group). Admission, discharge, and follow-up neurological assessments were accomplished according to the FIM instrument. Fifteen patients were excluded from review, leaving 130 patients (85 MP, 55 No-MP). The MP group was significantly younger than the No-MP group (30 yr versus 38 yr, $P < 0.05$). Although the mean trauma scores were similar between the two groups, the MP patients had a significantly lower injury severity score (ISS) than the No-MP patients ($P < 0.05$). The authors found no differences in mortality or neurological outcome between patients treated with methylprednisolone and those who were not. Despite older age and higher injury severity score, the No-MP group had better mobility at the time of hospital discharge. Admission mobility scores were similar (MP = 5.99 versus No-MP = 5.90), but the mobility scores differed significantly on hospital discharge (MP = 5.16 versus No-MP = 4.67, $P < 0.05$). The authors argued that the MP patient group had a more favorable opportunity for improvement than the No-MP patient group owing to younger age and lower ISS scores; however, neurological improvements in the MP group compared with the No-MP group were not observed. It is unclear from the study why most patients did not receive corticosteroid therapy, and this is the weakness of a nonrandomized study in which patient assignment to treatment may introduce bias. For example, an examination of the data indicates that the worst neurologically injured patients at admission were more likely to have received methylprednisolone. The findings of no difference in neurological examination improvement or functional recovery in this group seem to refute the findings of neurological improvement in NASCIS II patients who received methylprednisolone less than 8 hours after injury compared with those who did not receive the drug.

Gerndt et al (30), in 1997, reported a retrospective review of 231 patients with ASCI for the purpose of examining medical complications. Ninety-one patients were excluded because they received corticosteroids outside the NASCIS II protocol. One hundred forty patients were reviewed, comparing 93 patients who received methylprednisolone per the NASCIS II protocol with a historical control group of 47 patients who received no corticosteroid during treatment. The patient groups were similar with respect to age and injury severity. The authors found significant differences (increases) in the incidence of pneumonia ($P = 0.02$, 2.6-fold increase), particularly acute pneumonia ($P = 0.03$, 4-fold increase), ventilated days ($P = 0.04$), and ICU length of stay ($P = 0.045$) in methylprednisolone-treated patients compared with those who did not receive corticosteroids during treatment. Non-corticosteroid-treated patients had a higher incidence of urinary tract infections ($P = 0.01$). Methylprednisolone-treated patients had decreased general care floor length of stay ($P = 0.02$) and rehabilitation length of stay ($P = 0.035$). The authors concluded that methylprednisolone may increase the incidence of early infection, particularly pneumonia, in ASCI patients but has no adverse effect on long-term outcome. In 1997, Poynton et al (39) described 71 consecutive ASCI patients managed at the National Spinal Trauma Unit in Dublin, Ireland. They attempted a case-control analysis of ASCI patients treated with methylprednisolone ($n = 38$) compared with patients who did not receive methylprednisolone ($n = 25$) and provided follow-up from 13 months to 57 months after injury. Patients who did not receive methylprednisolone were referred more than 8 hours after injury. The authors concluded that multiple factors influenced outcome after ASCI. They found no difference in neurological outcome when they compared patients who received methylprednisolone with those who did not.

The results of the third NASCIS study (NASCIS III) were published in 1997 (16). NASCIS III was a double-blind randomized clinical trial comparing the efficacy of methylprednisolone administered for 24 hours with that of methylprednisolone administered for 48 hours. There was no placebo group. Entry criteria were similar to those described for NASCIS II study patients. Patients were assessed neurologically according to NASCIS I and II (change in motor and sensory scores) and by change in FIM at 6 weeks and 6 months. Four hundred ninety-nine patients were entered into the study, 166 in the 24-hour methylprednisolone group (24 MP), 167 in the 48-hour tirilazad mesylate group (48 TM), and 166 in the 48-hour methylprednisolone group (48MP). The authors reported that patients in the 48 MP group showed improved motor recovery at 6 weeks ($P = 0.09$) and at 6 months ($P = 0.07$) follow-up compared with 24 MP patients and 48 TM patients. When therapy was initiated between 3 and 8 hours after injury, the effect of the 48 MP regimen on change in motor score was significant at 6 weeks ($P = 0.04$) and at 6 months ($P = 0.01$) follow-up compared with patients in the 24 MP and 48 TM treatment groups. 48MP patients had more improvement in FIM at the 6-month follow-up ($P = 0.08$) compared with patients in the other two treatment groups. 48MP treatment patients also had higher rates of severe sepsis ($P = 0.07$) and severe pneumonia ($P = 0.02$). When treatment was initiated within 3 hours of injury, the same recovery pattern was observed in all three treatment groups. The authors concluded that patients with ASCI who receive methylprednisolone within 3 hours of injury should be maintained on the 24 MP regimen. When methylprednisolone is administered 3 to 8 hours after injury, they recommended the 48 MP regimen.

In 1998, the 1-year follow-up results of the NASCIS III trial were reported (17). The authors reported that for patients treated within 3 hours of injury, recovery rates at 1 year were equal in all three treatment groups. For patients treated between 3 and 8 hours after injury, 24 MP patients had diminished motor recovery and 48 MP patients had increased motor recovery at 1 year ($P = 0.053$). They noted no significant difference in functional outcome as measured by FIM in any treatment group. The authors concluded that if methylprednisolone is administered to patients with ASCI within 3 hours of injury, 24-hour maintenance is recommended. If methylprednisolone is administered 3 to 8 hours after injury, they recommended that a 48-hour maintenance regimen be followed. These final recommendations seem to be based on motor recovery score improvement alone ($P = 0.053$).

Predominant criticisms of the NASCIS III study and the reported results focus on three major issues: determination of optimum timing of therapy, method of motor assessment of SCI patients, and insignificant differences in motor recovery scores and functional outcome measures among study patients (18,19,32,33,37,51). For optimum timing of therapy, time-to-treatment data were not offered or explained. Like the 8-hour time for treatment cutoff “result” that came from the NASCIS II study, the “within 3 hours of injury” versus the “3 to 8 hours after injury” timeframes reported in NASCIS III seem arbitrary (18,32,37). It is not intuitive or likely that the 3-hour treatment time is an “all or nothing” time period supported by physiological evidence. With respect to the method of motor assessment and reporting, like the NASCIS II study, NASCIS III motor scores were reported as change in motor scores from the right side of the body. Left-side motor scores and total body motor scores were not provided. The failure to provide this study’s scientific evidence (particularly in light of the NASCIS I and II criticisms) suggests that the changes in right-side only motor scores are the only findings that approach significance at 1 year ($P = 0/053$) and argue against the meaningful nature of the data as interpreted and provided by the authors (18,32,37). Finally, the clinical significance of the changes in motor scores between groups, in light of the non-significant differences in patient function as determined by FIM scores, is not evident. NASCIS III patients who received 48 MP treatment had a 2-fold higher incidence of severe pneumonia, a 4-fold higher incidence of severe sepsis, and a 6-fold higher incidence of death due to respiratory complications than patients in the 24 MP treatment group (8,32). These differences, although not statistically significant, raise questions about the safety of the 48-hour treatment strategy proposed for patients with ASCI treated within 3 to 8 hours of injury. Additional important criticisms of the NASCIS III trial include those levied against both the NASCIS I and II studies (i.e., lack of standardized medical treatment, lack of a minimum motor impairment for inclusion [hence, normal motor

function patients admitted to the study], no vertebral level of injury cutoff, and unclear statistical methodology, analysis, and data interpretation) (18,32,37). NASCIS III was designed and implemented to be a randomized, double-blind clinical study in an attempt to generate Class I evidence on the efficacy of methylprednisolone, offered in two different treatment regimens, and tirilazad mesylate after ASCI in human subjects. The absence of evidence for functional improvement in any group argues against the clinical relevance of any of these regimens.

Wing, et al (49) examined the effect of methylprednisolone administered per the NASCIS II protocol on avascular necrosis (AVN) of the femoral heads of 91 ASCI patients, 59 who received the corticosteroid, and 32 who did not. The authors found no case of AVN in their study population and estimate the relative risk of AVN with high-dose 24-hour methylprednisolone therapy to be less than 5%.

In 2002, Pointillart et al (38) reported the results of a prospective, randomized clinical trial designed to evaluate the safety and effect of nimodipine, methylprednisolone, or both versus no pharmacological therapy in 106 ASCI patients. Patients were randomly assigned to one of four treatment groups, methylprednisolone per NASCIS II protocol (M), nimodipine (N), both methylprednisolone and nimodipine (MN), and neither medication (P). Blinded neurological assessment was accomplished via the American Spinal Cord Injury Association (ASIA) score at initiation of treatment and at 1-year follow-up. The authors performed early spinal decompression and stabilization as indicated. One hundred patients were available at 1-year follow-up. There was no significant difference in outcome among the four treatment groups for any of the ASIA scores recorded. Patients in all four treatment groups demonstrated significant neurological improvement at the 1-year follow-up compared with admission ($P < 0.0001$). Two-way analysis of variance revealed no interaction between methylprednisolone and nimodipine. There was a significant difference in recovery below the level of injury among patients with complete SCIs compared with those with incomplete injuries ($P < 0.0001$). Improvement among complete injury patients when present, involved the level of the lesion and the two adjacent caudal levels. The greatest neurological improvements were identified in incomplete injury patients. There was no significant difference in neurological outcome for patients who underwent surgery within 8 hours of injury, patients treated surgically between 8 and 24 hours after injury, and those managed without surgery. The incidence of infectious complications was higher among the patients treated with methylprednisolone compared with those who did not receive corticosteroids (66% versus 45%), but this difference was not significant. The authors concluded that pharmacological therapy offered no added benefits to patients with ASCIs. Unfortunately, sample size calculations are not provided by the authors, and therefore the statistical power of the study to show a significant benefit of the treatment(s) is unknown. In addition, indications for surgery and for timing of surgery were not provided, potentially adding bias. The failure to show a difference between groups in this study may be explained by these potential study design flaws.

A number of published critiques of the NASCIS data and their presentation in support of the use of methylprednisolone in the management of patients with ASCI have been offered (1,18,19,22,31-33a,35,37,40-42,44-46,51). A recent medical evidence-based review is provided by Short et al (46). These authors conclude, after review of the medical literature on the use of methylprednisolone for ASCI (animal and human experimental studies, including randomized human clinical trials), that the available evidence does not support the use of methylprednisolone in the treatment of ASCI. A number of reviews that support the use of methylprednisolone after ASCI have also been published, including a Cochrane Database of Systematic Reviews (3-5,6a,7,9,10,50).

In 2001, Matsumoto et al (36) reported their results of a prospective, randomized double-blind clinical trial comparing methylprednisolone with placebo in the treatment of patients with acute cervical SCI. The authors focused on potential medical complications after ASCI. Forty-six patients were included in the study: 23 treated with methylprednisolone per the NASCIS II protocol were compared

with 23 patients in a placebo treatment group. Complications associated with therapy were noted at 2-month follow-up. Patients treated with methylprednisolone had a higher incidence of complications compared with placebo-treated patients (56.5% versus 34.8%). Respiratory complications ($P = 0.009$) and gastrointestinal complications ($P = 0.036$) were the most significant between the two treatment populations. The authors concluded that patients with ASCI treated with methylprednisolone (particularly older patients) are at increased risk for pulmonary and gastrointestinal complications and deserve special care. This incidence of medical complications using methylprednisolone for 24 hours seems clinically important. The NASCIS III study demonstrated that these complications are even higher for 48-hour methylprednisolone administration as described above (17). This calls into question the use of corticosteroids for any timeframe, but especially for the 48-hour duration.

Finally, a review of the data in a large number of patients in the most recent GM-1 ganglioside trial who had methylprednisolone alone according to NASCIS II and III protocols did not confirm the findings of the NASCIS II and III trials (23). This is described in detail in the section below on the GM-1 ganglioside trials.

In summary, the available medical evidence does not support a significant clinical benefit from the administration of methylprednisolone in the treatment of patients after ASCI for either 24 or 48 hours duration. Three North American, multicenter randomized clinical trials have been completed and several other studies have been accomplished addressing this issue (11,13-17,21,28,29,38,39). The neurological recovery benefit of methylprednisolone when administered within 8 hours of ASCI has been suggested but not convincingly proven. The administration of methylprednisolone for 24 hours has been associated with a significant increase in severe medical complications. This is even more striking for methylprednisolone administered for 48 hours. In light of the failure of clinical trials to convincingly demonstrate a significant clinic benefit of administration of methylprednisolone, in conjunction with the increased risks of medical complications associated with its use, methylprednisolone in the treatment of acute human SCI is recommended as an option that should only be undertaken with the knowledge that the evidence suggesting harmful side effects is more consistent than the suggestion of clinical benefit.

GM-1 Ganglioside

GM-1 ganglioside has been evaluated in both animal and human studies of ASCI (2,26,27,47,48). In 1991, Geisler et al (25) described the results of a prospective, randomized placebo-controlled, double-blind trial of GM-1 ganglioside in the treatment of human patients with ASCI. Of 37 patients entered into the study, 34 were available for 1-year follow-up (16 GM-1 patients, 18 placebo). All patients received a 250-mg bolus of methylprednisolone and then 125 mg every 6 hours for 72 hours. GM-1 patients were administered 100 mg of GM-1 ganglioside per day for 18 to 32 days, with the first dose provided within 72 hours of injury. Neurological evaluation was accomplished with Frankel scale and ASIA motor score assessments. The authors reported that GM-1 ganglioside treated patients had significant improvements in the distribution of Frankel grades from baseline to 1-year follow-up ($P = 0.034$) and significantly improved ASIA motor scores compared with placebo-treated patients ($P = 0.047$) (26,27). The recovery of motor function in GM-1 ganglioside-treated patients was thought to be caused by recovery of strength in paralyzed muscles rather than strengthening of paretic muscles. There were no adverse effects attributed to the administration of the study drug. The authors concluded that GM-1 ganglioside enhances neurological recovery in human patients after SCI and deserves further study.

In 1992, a multicenter GM-1 ganglioside ASCI study was initiated. It was a prospective, double-blind randomized and stratified trial that enrolled 797 patients by study end in early 1997 (23). All patients received methylprednisolone per the NASCIS II protocol. Patients were randomized into three initial study groups: placebo, low-dose GM-1 (300-mg loading dose and then 100 mg/d for 56 d), and

high-dose GM-1 (600-mg loading dose and then 200 mg/d for 56 d). Placebo or GM-1 was administered at the conclusion of the 23-hour methylprednisolone infusion. Patients were assessed using the modified Benzel Classification and the ASIA motor and sensory examinations a 4, 8, 16, 26, and 52 weeks after injury. Aggressive medical and surgical management paradigms were used. Patients had to have an acute, nonpenetrating SCI (anatomic vertebral level C2 through T11) of at least moderate severity (no neurologically normal or nearly normal patients). The primary efficacy assessment was the proportion of patients who improved at least two grades from baseline examination (defined as “marked recovery”), at Week 26 of the study. Secondary efficacy assessments included the time course of marked recovery, the ASIA motor score, and ASIA sensory evaluations, relative and absolute sensory levels of impairment, and assessments of bladder and bowel function. A planned interim analysis of the first 180 patients resulted in the addition of stratification by patient age and discontinuation of the high-dose GM-1 treatment strategy because of an early trend for higher mortality. At the study conclusion, 37 patients were judged ineligible, leaving 760 patients for primary efficacy analysis. The authors found no significant difference in mortality between treatment groups (23). The authors did not identify a higher proportion of patients with marked recovery in motor function at 26 weeks when they compared GM-1 treated patients to the placebo treatment group in their primary efficacy analysis. The time course of recovery indicated earlier attainment of marked recovery in GM-1-treated patients. The authors concluded that, despite the lack of statistical significance in the primary analysis, numerous positive secondary analyses indicate that GM-1 ganglioside is a useful drug in the management of ASCI (23). The placebo group within this study of GM-1 represents a group of 322 patients who received methylprednisolone within 8 hours of injury. Of interest, these 322 patients (measured in a similar, albeit, more detailed manner as NASCIS II patients) did not demonstrate the previously published neurological examination improvement found in 62 NASCIS II patients treated within the same timeframe (13,14). Similarly, 218 of these patients received 24 hours methylprednisolone treatment within 3 hours of injury, as suggested in NASCIS III, and did not show the same neurological examination motor improvement as the 75 NASCIS III patients who received the same regimen (16,17). The authors could not confirm the NASCIS findings that timing of methylprednisolone therapy had an impact on spinal cord recovery. This further brings into question the conclusions of the NASCIS II and III methylprednisolone trials.

In summary, the available medical evidence does not support a significant clinical benefit from the administration of GM-1 ganglioside in the treatment of patients after ASCI. Two North American multicenter, randomized clinical trials have been completed addressing this issue (23,29). The neurological recovery benefit of GM-1 ganglioside when administered for 56 days after the administration of methylprednisolone within 8 hours of ASCI has been suggested but not convincingly proven. At present, GM-1 ganglioside (a 300-mg loading dose and then 100 mg/d for 56 d), when initiated after the administration of methylprednisolone given within 8 hours of injury (NASCIS II protocol), is recommended as an option in the treatment of adult patients with ASCI.

KEY ISSUES FOR FUTURE INVESTIGATION

Given the problems associated with the many trials attempting to answer the questions surrounding the use of pharmacological agents in acute spinal cord-injured patients, it is clear that more research is required. Issues such as adequate numbers of patients to achieve statistical power, a placebo group as one of the treatment arms, standardized medical and surgical protocols to diminish bias, careful collection of relevant outcome data, especially functional outcomes, and appropriate statistical analyses need to be further addressed a priori. Research into all potentially promising pharmacological agents, including, but not limited to, tirilazad mesylate, naloxone, methylprednisolone, and GM-1 should be undertaken.

REFERENCES

1. Acland RH, Anthony A, Inglis GS, Walton DI, Xiong X: Methylprednisolone use in acute spinal cord injury. **N Z Med J** 9:99, 2001 (letter).
2. Amar PA, Levy ML: Pathogenesis and pharmacological strategies for mitigating secondary damage in acute spinal cord injury. **Neurosurgery** 44:1027-1040, 1999.
3. Bracken MB: National Acute Spinal Cord Injury Study of methylprednisolone or naloxone. **Neurosurgery** 28:628-629, 1991 (letter).
4. Bracken MB: Methylprednisolone and spinal cord injury. **J Neurosurg** 93:175-177, 2000 (letter).
5. Bracken MB: The use of methylprednisolone. **J Neurosurg** 93:340-341, 2002 (letter).
6. Bracken MB: High dose methylprednisolone must be given for 24 or 48 hours after acute spinal cord injury. **BMJ** 322:862-863, 2001 (letter).
- 6a. Bracken MB: Methylprednisolone and acute spinal cord injury: An update of the randomized evidence. **Spine** 26(24Suppl):S47-S54, 2001.
7. Bracken MB: Pharmacological interventions for acute spinal cord injury. **Cochrane Database Syst Rev** 1:1-32, 2001.
8. Bracken MB, Holford TR: Effects of timing of methylprednisolone or naloxone administration on recovery of segmental and long-tract neurological function NASCIS 2. **J Neurosurg** 79:500-507, 1993.
9. Bracken MB, Holford TR: Response: Treatment of spinal cord injury. **J Neurosurg** 80:954-955, 1994 (letter).
10. Bracken MB, Aldrich EF, Herr DL, Hitchon PW, Holford TR, Marshall LF, Nockels RP, Pascale V, Shepard MJ, Sonntag VKH, Winn HR, Young W: Clinical measurement, statistical analysis and risk-benefit: Controversies from trials of spinal injury. **J Trauma** 48:558-561, 2000.
11. Bracken MB, Collins WF, Freeman DF, Shepard MJ, Wagner FW, Silten RM, Hellenbrand KG, Ransohoff J, Hunt WE, Perot PL Jr, Grossman RG, Green BA, Eisenberg HM, Rifkinson N, Goodman JH, Meagher JN, Fischer B, Clifton GL, Flamm ES, Rawe SE: Efficacy of methylprednisolone in acute spinal cord injury. **JAMA** 251:45-52, 1984.
12. Bracken MB, Shepard MJ, Collins WF, Holford TR, Baskin DS, Flamm E, Eisenberg HM, Leo-Summers L, Maroon JC, Marshall LF, Perot PL Jr, Piepmeier J, Sonntag VKH, Wagner FC Jr, Wilberger JL, Winn HR, Young W: Response: Methylprednisolone for spinal cord injury. **J Neurosurg** 77:325-327, 1992 (letter).
13. Bracken MB, Shepard MJ, Collins WF, Holford TR, Baskin DS, Flamm E, Eisenberg HM, Leo-Summers L, Maroon JC, Marshall LF, Perot PL Jr, Piepmeier J, Sonntag VKH, Wagner FC Jr, Wilberger JE, Winn HR, Young W: Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data – Results of the Second National Acute Spinal Cord Injury Study. **J Neurosurg** 76:23-31, 1992.

14. Bracken MB, Shepard MJ, Collins WF, Holford TR, Young W, Baskin DS, Eisenberg HM, Flamm E, LeoSummers L, Maroon J, Marshall LF, Perot PL Jr, Piepmeier J, Sonntag VKH, Wagner FC, Wilberger JE, Winn HR: A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal cord injury: Results of the Second National Acute Spinal Cord Injury Study (NASCIS-2). **N Engl J Med** 322:1405-1411, 1990.
15. Bracken MB, Shepard MJ, Hellenbrand KG, Collins WF, Leo-Summers L, Freeman DF, Wagner FC, Flamm ES, Eisenberg HM, Goodman JH, Perot PL JR, Green BA, Grossman RG, Meagher JN, Young W, Fischer B, Clifton GL, Hunt WE, Rifkinson N: Methylprednisolone and neurological function 1 year after spinal cord injury: Results of the National Acute Spinal Cord Injury Study. **J Neurosurg** 63:704-713, 1985.
16. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings M, Herr DL, Hitchon PW, Marshall LF, Nockels RP, Pascale V, Perot PL Jr, Piepmeier JM, Sonntag VKH, Wagner F, Wilberger JE, Winn HR, Young W: Administration of methylprednisolone for 24 or 48 hours or tirilazad mesylate for 48 hours in the treatment of acute spinal cord injury: Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial – National Acute Spinal Cord Injury Study. **JAMA** 277:1597-1604, 1997.
17. Bracken MB, Shepard MJ, Holford TR, Leo-Summers L, Aldrich EF, Fazl M, Fehlings MG, Herr DL, Hitchon PW, Marshall LF, Nockels RP, Pascale v, Perot PL Jr, Piepmeier JM, Sonntag VKH, Wagner F, Wilberger JE, Winn HR, Young W: Methylprednisolone or tirilazad mesylate administration after acute spinal cord injury: 1-year follow up – Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. **J Neurosurg** 89:699-706, 1998.

18. Coleman WP, Benzel D, Cahill DW, Ducker T, Geisler F, Green B, Gropper MR, Goffin J, Madsen PW III, Maiman DJ, Ondra SL, Rosner MJ, Sasso RC, Trost GR, Zeidman S: A critical appraisal of the reporting of the National Acute Spinal Cord Injury Studies (II and III) of methylprednisolone in acute spinal cord injury. **J Spinal Disord** 13:185-199, 2002.
19. Ducker TB, Zeidman SM: Spinal cord injury: Role of steroid therapy. **Spine** 19:2281-2287, 1994.
20. Duh MS, Shepard MJ, Wilberger JE, Bracken MB: The effectiveness of surgery on the treatment of acute spinal cord injury and its relation to pharmacological treatment. **Neurosurgery** 35:240-249, 1994.
21. Galandiuk S, Raque G, Appel S, Polk HC Jr: The two-edged sword of large-dose steroids for spinal cord trauma. **Ann Surg** 218:419-427, 1993.
22. Geisler FH: Commentary on NASCIS-2. **J Spinal Disord** 5:132-133, 1992 (comment).
23. Geisler FH, Coleman WP, Grieco G, Dorsey FC, Poonian D, The Sygen Study Group: The GM-1 ganglioside multi-center acute spinal cord injury study. **Spine** 26(24 Suppl):S87-S98, 2001.
24. Geisler FH, Dorsey FC, Coleman WP: Correction: Recovery of motor function after spinal cord injury – A randomized, placebo-controlled trial with GM-1 ganglioside. **N Eng J Med** 324:1659-1660, 1991.
25. Geisler FH, Dorsey FC, Coleman WP: Recovery of motor function after spinal cord injury – A randomized, placebo-controlled trial with GM-1 ganglioside. **N Eng J Med** 324:1829-1838, 1991.
26. Geisler FH, Dorsey FC, Coleman WP: GM-1 ganglioside in human spinal cord injury. **J Neurotrauma** 9(Suppl 2):S517-S530, 1992.
27. Geisler FH, Dorsey FC, Coleman WP: GM-1 ganglioside for spinal cord injury. **N Engl J Med** 326:494, 1992.
28. George ER, Scholten DJ, Buechler CM, Jordan-Tibbs J, Mattice C, Albrecht RM: Failure of methylprednisolone to improve the outcome of spinal cord injuries. **Am Surg** 61:659-664, 1995.
29. Gerhart KA, Johnson RL, Menconi J, Hoffman RE, Lammertse DP: Utilization and effectiveness of methylprednisolone in a population-based sample of spinal cord injured persons. **Paraplegia** 33:316-321, 1995.
30. Gerndt SJ, Rodriguez JL, Pawlik JW, Taheri PA, Wahl WL, Micheals AJ, Papadopoulos SM: Consequences of high-dose steroid therapy for acute spinal cord injury. **J Trauma** 42:279-284, 1997.
31. Hanigan WC, Anderson RJ: Commentary on NASCIS-2. **J Spinal Disord** 5:125-131, 1992.
32. Hurlbert RJ: Methylprednisolone for acute spinal cord injury: An inappropriate standard of care. **J Neurosurg** 93(Suppl 1):1-7, 2001.
33. Hurlbert RJ: The use of methylprednisolone. **J Neurosurg** 93(Suppl 1):340-341, 2000 (letter).

- 33a. Hurlbert RJ: The role of steroids in acute spinal cord injury: An evidence-based analysis. *Spine* 26(24 Suppl):S39-S46, 2001.
34. Landi G, Ciccone A: GM-1 ganglioside for spinal cord injury. *N Eng J Med* 326:493, 1992 (letter).
35. Lyons MK, Partington MD, Meyer FB: A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. *N Eng J Med* 323:1207-1208, 1990.
36. Matsumoto T, Tamaki T, Kawakami M, Yoshida M, Ando M, Yamada H: Early complications of high-dose methylprednisolone sodium succinate treatment in the follow-up of acute-cervical spinal cord injury. *Spine* 26:426-430, 2001.
37. Nesathurai S: Steroids and spinal cord injury: Revisiting the NASCIS 2 and NASCIS 3 trials. *J Trauma* 45:1088-1093, 1998.
38. Pointillart V, Petitjean ME, Wiart L, Vital JM, Lassie P, Thicolpe M, Dabadie P: Pharmacological therapy of spinal cord injury during the acute phase. *Spinal Cord* 38:71-76, 2002.
39. Poynton AR, O'Farrell DA, Shannon F, Murray P, McManus F, Walsh MG: An evaluation of the factors affecting neurological recovery following spinal cord injury. *Injury* 28:545-548, 1997.
40. Rosner MJ: National acute spinal cord injury study of methylprednisolone or naloxone. *Neurosurgery* 28:628, 1991 (letter).
41. Rosner MJ: Methylprednisolone for spinal cord injury. *J Neurosurg* 77:324-325, 1992.
42. Rosner MJ: Treatment of spinal cord injury. *J Neurosurg* 80:954-955, 1994.
43. Schonhofer PS: GM-1 ganglioside for spinal cord injury. *N Eng J Med* 326:493, 1992 (letter).
44. Shapiro SA: Methylprednisolone for spinal cord injury. *J Neurosurg* 77:324-327, 1992.
45. Short DJ: Use of steroids for acute spinal cord injury must be reassessed. *BMJ* 321:1224, 2000 (letter).
46. Short DJ, El Masry WS, Jones PW: High dose methylprednisolone in the management of acute spinal cord injury: A systemic review from a clinical perspective. *Spinal Cord* 38:273-286, 2002.
47. Tator CH: Experimental and clinical studies of the pathophysiology and management of acute spinal cord injury. *J Spinal Cord Med* 19:206-214, 1996.
48. Tator CH: Biology of neurological recovery and functional restoration after spinal cord injury. *Neurosurgery* 42:696-708, 1998.
49. Wing PC, Nance P, Connell DG, Gagnon F: Risk of avascular necrosis following short term megadose methylprednisolone treatment. *Spinal Cord* 36:633-636, 1998.

50. Young W, Bracken MB: The Second National Acute Spinal Cord Injury Study. **J Neurotrauma** 9(Suppl 1):S397-S405, 1992.
51. Zeidman SM, Ling GS, Ducker TB, Ellenbogen RG: Clinical applications of pharmacologic therapies for spinal cord injury. **J Spinal Disord** 9:367-380, 1996.

TABLE 9.1 Summary of Reports on Treatment with Methylprednisolone after Acute Cervical Spinal Cord Injury*

Series (Ref No)	Description of Study	Evidence Class	Conclusions
Bracken et al, 1984 (11)	Multicenter, double-blind randomized trial comparing MP (2000 mg/d versus 100 mg/d for 11 d) in treatment of 330 ASCI patients (NASCIS I study).	III (study design, data presentation, interpretation and analysis flaws)	No treatment effect at 6 wk and 6 mo post-injury. No control group.
Bracken et al, 1985 (15)	1-yr follow-up of NASCIS I study.	III (study design, data presentation, interpretation and analysis flaws)	No significant difference in neurological recovery of motor or sensory function 1-yr post-injury.
Bracken et al, 1990 (14)	Multicenter, randomized, double-blind, placebo-controlled trial comparing MP with naloxone and placebo in treatment of 487 ASCI patients (NASCIS II study).	III (study design, data presentation, interpretation and analysis flaws)	Significant improvement in motor change scores ($P = 0.03$), and sensation change scores ($P = 0.02$) at 6 mo post-injury for patients treated with MP within 8 h of injury.
Bracken et al, 1992 (13)	1-yr follow-up of NASCIS II study.	III (study design, data presentation, interpretation and analysis flaws)	Significant improvement in motor changes scores 1 year post-injury for patients treated with MP within 8 h of injury ($P = 0.03$). Administration of MP detrimental if given more than 8 h after injury.
Galandiuk et al, 1993 (21)	Prospective assessment of 15 patients from 1990 to 1993 with retrospective review of 17 patients from 1987 to 1990 to assess differences in treatment outcome with MP compared with treatment without corticosteroids.	III	No difference in neurological outcome between two sets of patients. MP patients had immune response alterations, higher rate of pneumonia, and longer hospital stays than patients who did not receive corticosteroids.
Gerhart et al, 1995 (29)	Concurrent cohort comparison study (population-based) of 363 ASCI patients managed from 1990 to 1991 and 1993. 188 patients managed with NASCIS II MP compared with 90 patients with no MP.	III (Inadequate statistical power)	No differences in neurological outcome using Frankel classification between MP and No-MP patients. However, may be insufficient numbers of patients to show significant differences.
George et al, 1995 (28)	Retrospective review of 145 ASCI patients, 80 treated with MP compared with 65 who did not receive MP.	III	No difference in mortality or neurological outcome between groups despite younger age, less severe injury in MP-treated patients.
Gerndt et al, 1997 (30)	Retrospective review with historical control of 231 ASCI patients, 91 excluded. Comparison of medical complications among 93 MP patients compared with 47 who received no corticosteroid.	III	MP-treated patients had significant increases in pneumonia ($P = 0.02$), acute pneumonia ($P = 0.03$), ventilated days ($P = 0.04$), and ICU stay ($P = 0.45$), but no adverse effect on long-term outcome.
Poynton et al, 1997 (39)	Case-control analysis of 71 consecutive ASCI admissions. 63 available for 13 mo to 57 mo follow-up. 38 patients treated with MP compared with 25 referred > 8 hr after injury who received no MP.	III	Multiple factors influence recovery after SCI. No effect of MP or surgery on outcome.

Series (Ref No)	Description of Study	Evidence Class	Conclusions
Bracken et al, 1997 (16)	Multicenter, randomized double-blind trial comparing MP administered for 24 hr to MP administered 48 hr and TM in the treatment of 499 ASCI patients (NASCIS III study).	III (study design, data presentation, interpretation and analysis flaws)	48 MP patients had improved motor recovery at 6 wk and at 6 mo compared with 24 MP and 48 TM groups NS. When treatment initiated between 3 h and 8 h after injury, 48 MP had significant improvement of motor scores at 6 wk (P = 0.04) and 6 mo (P = 0.01). 48 MP was associated with high rates of sepsis and pneumonia. No control group.
Bracken et al, 1997 (17)	1-yr follow-up of NASCIS III study.	III (study design, data presentation, interpretation and analysis flaws)	Recovery rates equal in all 3 groups when treatment initiated within 3 h of injury. When treatment initiated between 3 h and 8 h, 24 MP patients had diminished recovery, 48 MP patients had increased motor recovery (P = 0.053).
Pointillart et al, 2000 (38)	Multicenter, prospective, randomized clinical trial of 106 ASCI patients treated with MP, nimodipine, neither, or both.	III (Inadequate statistical power)	No significant difference in neurological outcome at 1-yr follow-up between groups. Incomplete ASCI had significant improvement below level of injury compared to complete patients (P < 0.0001). Higher incidence of infectious complications among patients receiving corticosteroids (NS).
Matsumoto et al, 2001 (36)	Prospective randomized, double-blind study comparing incidence of medical complications among 46 ASCI patients, 23 treated with MP, 23 with placebo.	I	MP patients had higher incidence of complications (56.5% versus 34.8%). Respiratory complications (P = 0.009) and gastrointestinal bleed (P = 0.036) were most significant between groups. No data on neurological improvement.

*ASCI, acute spinal cord injury; NASCIS National Acute Spinal Cord Injury Study; MP, methylprednisolone; ICU, intensive care unit; SCI, spinal cord injury; TM tirilazad mesylate; NS, not significant.

Table 9.2 Summary of Reports on Treatment with GM-1 Ganglioside after Acute Spinal Cord Injury.

Series (Ref No)	Description of Study	Evidence Class	Conclusions
Geisler et al, 1991 (25)	Prospective, randomized, double-blind trial of GM-1 ganglioside in 37 human ASCI patients. All received 250-mg MP bolus followed by 125 mg ever 6 h x 72 h before randomization (placebo group)	I	GM-1 ganglioside enhances recovery of neurological function, significant difference in recovery compared with MP group (P = 0.047). Insufficient numbers of patients to draw meaningful conclusions. No true placebo group.
Geisler et al, 2001 (23)	Prospective, randomized, double-blind stratified multicenter trial of GM-1 ganglioside in 760 ASCI patients. All received MP per NASCIS II protocol (placebo group).	I	No significant differences in neurological recovery identified between GM-1 treated patients and MP-treated patients at 26-wk follow-up. Trend for earlier recovery in GM-1-treated patients. No true placebo group.

*ASCI, acute spinal cord injury; NASCIS National Acute Spinal Cord Injury Study; MP, methylprednisolone