Background

Attacks or relapses are the dominating feature of relapsing–remitting multiple sclerosis (MS), but are also observed in patients with secondary progressive MS with superimposed relapses. Even patients with primary progressive MS may experience relapses, becoming progressive-relapsing MS [1, 2]. In the McDonald criteria for the diagnosis of MS, a relapse is defined as ‘an episode of neurological disturbance of the kind seen in MS, when the clinicopathological studies have established that the causative lesions are inflammatory and demyelinating in nature’ [3, 4]. An attack should last for at least 24 h and, according to the McDonald criteria, there should be expert opinion that the event is not a pseudoattack as might be caused by an increase in body temperature or infection. Although the majority of relapses improve to some extent, incomplete recovery is an important determinant of irreversible, or at least long-lasting, neurological impairment in relapsing–remitting MS [5, 6].

Glucocorticoid treatment is recommended as the first-line treatment of MS relapses in North American guidelines and in the recommendations of a European MS therapy consensus group [7, 8]. The aim of the European Federation of Neurological Societies (EFNS) task force was to review the current literature on relapse treatment. Key issues addressed are whether treatment of MS relapses: (1) can improve the speed of recovery; (2) can influence long-term recovery; (3) can influence subsequent disease activity; (4) has significant side effects. Furthermore, the task force sought to provide guidelines on whether all relapses should be treated and how relapses during pregnancy should be managed.

Search strategy

We searched literature databases (EMBASE and PubMed), in English, for papers using the search terms ‘multiple sclerosis’, ‘attack’, ‘relapse’, ‘exacerbation’, and ‘treatment’ in November 2004 and November 2009. The Cochrane Library and the reference lists of individual papers were searched for studies not identified in the EMBASE and PubMed searches. Studies of various treatments for patients suffering from relapses of MS were considered for the guidelines and were rated as Class I to Class IV studies according to the recommendations for EFNS scientific task forces [9].

Method for reaching consensus

The results of the literature searches were circulated by email to the task force members for comments. The task force chairman prepared a first draft of the manuscript based on the results of the literature review and comments from the task force members. The draft and the recommendations were discussed during telephone conferences until consensus was reached within the task force.
force. Recommendations were rated from A to C according to the EFNS guidelines for scientific task forces [9]. Where there was insufficient evidence to support firm recommendations the term ‘Good Practice Point’ (GPP) was used.

**Results**

**Effect of glucocorticoid and adrenocorticotrophic hormone (ACTH) treatment on MS relapses**

Glucocorticoid or ACTH treatment of MS relapses was analysed in a Cochrane review that included results from six randomized, placebo-controlled clinical trials of either ACTH (two trials), intravenous (i.v.) methylprednisolone treatment (three trials) or oral methylprednisolone treatment (one trial) [10–15]. All trials reported a benefit in terms of rate of recovery compared to placebo [16]. A similar conclusion was reached in another meta-analysis, which used less stringent criteria for study inclusion than the Cochrane review [17].

Three trials have compared the efficacy of i.v. methylprednisolone and ACTH treatment in MS relapses [18–20]. One study including 14 patients treated with i.v. methylprednisolone (1 g daily for 7 days) and 11 patients treated with intramuscular (IM) ACTH (80 units, 60 units, 40 units, and 20 units daily, each for 1 week) reported more rapid improvement (after 3 and 28 days) after i.v. methylprednisolone than after ACTH treatment, but there was no significant difference after 3 months [19]. However, the patient blinding and the primary outcome were not clearly defined, for which reason this study should be considered a Class III study. One Class II study compared the administration of 1 g of methylprednisolone once daily for 3 days to ACTH treatment (80 units for 7 days, 40 units for 4 days and 20 units for 3 days) in 61 patients, and found no difference in terms of rate of recovery or final outcome after 12 weeks [20]. A Class III study including 60 patients, treated with either i.v. methylprednisolone (20 mg/kg day 1–3, 10 mg/kg day 4–7, 5 mg/kg day 8–10, and 1 mg/kg day 11–15) or ACTH (1 mg i.v. daily for 15 days), also found no difference in the efficacy of ACTH and methylprednisolone treatment [18]. The studies found no major differences in adverse events between methylprednisolone and ACTH treatment. Thus there is no evidence of any major difference in the efficacy of ACTH and methylprednisolone treatment from comparative studies, but the clinical trials were too small to rule out some difference in efficacy. Indeed, in the Cochrane review it was suggested that methylprednisolone treatment could still confer greater benefit than treatment with ACTH, and the administration of methylprednisolone is simpler than the more prolonged ACTH treatment regimen [16].

In a separate meta-analysis of three double-blind, randomized, placebo-controlled trials [21], it was concluded that treatment with i.v. methylprednisolone (15 mg/kg day 1–3, 10 mg/kg day 4–6, 5 mg/kg day 7–9, 2.5 mg/kg day 10–12, 1 mg/kg day 13–15 followed by oral prednisone tapered slowly over 120 days [10]), i.v. methylprednisolone without a tapering dose (500 mg once daily for 5 days [13]), or oral methylprednisolone (500 mg once daily for 5 days followed by 400, 300, 200, 100, 64, 48, 32, 16, 8, and 8 mg once daily the subsequent 10 days [15]) resulted in significantly faster recovery than did treatment with placebo (table 27.1). The first two trials provided follow-up data in a placebo-controlled design for 15 days [10] and 28 days [13]. The oral methylprednisolone study found significant differences between the methylprednisolone and the placebo group after 8 weeks and a trend to better improvement in the methylprednisolone group after 1 year [15]. In the latter trial there was no evidence that the 1-year risk of subsequent relapses was influenced by oral high-dose methylprednisolone treatment.

**Specific glucocorticoids, dose, and route of administration**

The clinical trials of glucocorticoid treatment in relapses of MS have mainly assessed the effect of methylprednisolone treatment. Two trials have compared the effect of methylprednisolone treatment given i.v. or orally. One Class III study compared the effect of methylprednisolone (500 mg once daily for 5 days) given orally or i.v. in 35 patients with an MS relapse, and found no significant difference in recovery between the two treatment arms after 5 and 28 days [22]. Another study (Class I) compared the effect of oral methylprednisolone (48 mg daily for 7 days, 24 mg daily for 7 days, and 12 mg daily for 7 days) to treatment with i.v. methylprednisolone (1 g daily for 3 days) [23]. In this study, recovery from the relapse was similar in the 38 patients in the i.v. treatment group and the 42 patients in the oral treatment group at all time points for
Table 27.1 Summary of three randomized, placebo-controlled trials comparing methylprednisolone (MP) treatment to placebo in patients with relapses of MS (Durelli et al. [10]; Milligan et al. [12]; Sellebjerg et al. [15]). Data are changes in Kurtzke EDSS scores from baseline (mean and standard deviation in brackets) or differences (mean and 95% confidence intervals in brackets) between MP and placebo reported in a meta-analysis (Miller et al. [21]).

<table>
<thead>
<tr>
<th>Study and treatment</th>
<th>Change from baseline</th>
<th>Difference (MP vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 5–7</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durelli, placebo (n = 8)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>i.v. methylprednisolone (n = 12)</td>
<td>−1.00 (0.6)</td>
<td>−1.00 (−1.45 to −0.55)</td>
</tr>
<tr>
<td>Milligan, placebo (n = 9)</td>
<td>−0.28 (0.51)</td>
<td></td>
</tr>
<tr>
<td>i.v. methylprednisolone (n = 13)</td>
<td>−1.46 (1.38)</td>
<td>−1.18 (−2.19 to −0.17)</td>
</tr>
<tr>
<td>Sellebjerg, placebo (n = 25)</td>
<td>−0.06 (0.44)</td>
<td></td>
</tr>
<tr>
<td>Oral methylprednisolone (n = 26)</td>
<td>−0.58 (0.82)</td>
<td>−0.52 (−0.89 to −0.14)</td>
</tr>
<tr>
<td>Pooled difference:</td>
<td></td>
<td>−0.76 (standard error 0.14)</td>
</tr>
<tr>
<td><strong>Day 21–28</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durelli, placebo (n = 8)</td>
<td>−0.38 (0.52)</td>
<td></td>
</tr>
<tr>
<td>i.v. methylprednisolone (n = 12)</td>
<td>−2.04 (1.48)</td>
<td>−1.67 (−2.82 to −0.51)</td>
</tr>
<tr>
<td>Milligan, placebo (n = 8)</td>
<td>−0.25 (1.22)</td>
<td></td>
</tr>
<tr>
<td>i.v. methylprednisolone (n = 13)</td>
<td>−2.04 (1.51)</td>
<td>−1.79 (−3.11 to −0.46)</td>
</tr>
<tr>
<td>Sellebjerg, placebo (n = 25)</td>
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<td></td>
</tr>
<tr>
<td>Oral methylprednisolone (n = 26)</td>
<td>−0.94 (0.90)</td>
<td>−0.56 (−1.04 to −0.08)</td>
</tr>
<tr>
<td>Pooled difference:</td>
<td></td>
<td>−0.85 (standard error 0.21)</td>
</tr>
</tbody>
</table>

up to 24 weeks of follow-up. The relapse rate the following 2 years was also similar in the oral and i.v. treatment group [24]. A Class III study comparing the effect of i.v. and oral methylprednisolone (1000 mg daily for 5 days) in 40 patients found comparable effect of the two treatment regimens on magnetic resonance imaging (MRI) outcomes [25]. A recent Cochrane review concluded that oral and i.v. treatment are both efficacious with respect to clinical outcomes (relapse recovery and subsequent relapse activity), radiological outcomes, and bioavailability measures, but that there is still insufficient evidence to prove equivalence of oral and i.v. treatment [26].

Oral tapering doses of glucocorticoids are commonly used, but no randomized controlled studies have yet compared the outcome of an acute relapse in patients treated with tapering doses of glucocorticoids or placebo following short-term, high-dose methylprednisolone treatment. However, a recent Class III study found no difference in recovery rate in 152 patients treated with high-dose methylprednisolone followed by an oral prednisone taper and 112 patients treated with high-dose methylprednisolone only [27].

Three studies have compared i.v. methylprednisolone treatment given in different doses. One Class III study found that recovery was faster after treatment with i.v. methylprednisolone (1 g once daily for 5 days) than after a single 1 g dose of i.v. methylprednisolone [28]. Two other studies (both Class III) have compared the effect of different doses of i.v. methylprednisolone in relapses of MS on a panel of different outcome measures. In the first study, treatment with i.v. methylprednisolone at a dose of 500 mg once daily for 5 days was compared to treatment with 2000 mg once daily for 5 days in 31 patients with a relapse of MS [29]. There was no difference in the efficacy of the low dose and the high dose of methylprednisolone in terms of clinical recovery or short-term suppression of MRI disease activity, but it was suggested that the high dose resulted in more pronounced suppression of MRI disease activity after 1 and 2 months. In the second study, i.v. methylprednisolone at a dose of 1 g or 2 g once daily for 5 days was compared in 24 patients who were followed up with clinical and neurophysiologic studies for 21 days after randomization to one of the two treatment arms [30]. This study showed no significant differences between the two methylprednisolone doses on the majority of diverse outcome measures, but a few favoured the higher dose over the lower dose. Two studies have compared the effect of treatment with different...
doses of methylprednisolone and dexamethasone in relapses of MS [31, 32]. Due to the small sample sizes and differences in the baseline characteristics of the patients randomized to the different treatment arms, the results of these two studies are difficult to interpret.

**Glucocorticoid treatment of acute optic neuritis**

In the North American Optic Neuritis Treatment Trial (ONTT), 457 patients were randomized to receive treatment with i.v. methylprednisolone (250 mg four times daily for 3 days followed by oral prednisone, 1 mg/kg for 11 days, 20 mg on day 15, and 10 mg on days 16 and 18), oral prednisone (1 mg/kg for 14 days, 20 mg on day 15, and 10 mg on days 16 and 18), or oral placebo [33]. Treatment allocation was not blinded in patients randomized to treatment with i.v. methylprednisolone, while prednisone treatment and placebo was given in a double-blind design. Thus, the study was a Class II study investigating the efficacy of methylprednisolone treatment, but a Class I study in the comparison of oral prednisone and placebo. The study found no significant effect of i.v. methylprednisolone or oral prednisone treatment on the recovery of visual acuity, but the recovery of contrast sensitivity and visual fields was significantly faster in patients treated with i.v. methylprednisolone. After 6 months, patients treated with i.v. methylprednisolone had still recovered slightly better than patients treated with placebo, but no significant treatment effect was seen at follow-up after 1 year [34]. Oral prednisone treatment had no effect on the recovery from acute optic neuritis in either the ONTT or a Danish Class I study of oral prednisolone versus placebo in 128 patients with acute optic neuritis ([33], J.L. Frederiksen, personal communication). Treatment with oral methylprednisolone (100 mg, 80 mg, 60 mg, 40 mg, 30 mg, 20 mg, 10 mg, and 5 mg daily for 3 days each) was not better than treatment with oral thiamine (100 mg daily for 24 days) on any of several outcome measures in a Class II study including 38 patients with acute optic neuritis [35].

Two additional studies (Class I) have compared the effect of treatment with high-dose methylprednisolone in acute optic neuritis. One study included 60 patients with acute optic neuritis who were treated with oral high-dose methylprednisolone (500 mg once daily for 5 days followed by 400, 300, 200, 100, 64, 48, 32, 16, 8, and 8 mg once daily the subsequent 10 days) or oral placebo [36]. Oral methylprednisolone treatment resulted in significantly better recovery of spatial visual function (visual acuity and contrast sensitivity), colour vision function, and visual symptoms after 1 week, but only borderline significant effects were observed after 3 weeks, and after 8 weeks there was no evidence of an effect of oral methylprednisolone treatment [36]. In a study of 66 patients with acute optic neuritis treatment with i.v. methylprednisolone (1 g once daily for 3 days) did not improve the outcome from acute optic neuritis after 26 weeks on either a panel of visual function and neurophysiologic variables or on MRI outcome measures [37].

A controversial finding in the ONTT was that patients treated with i.v. methylprednisolone appeared to have a lower risk of developing MS during 2 years of follow-up than patients treated with placebo. This was not statistically significant in the original trial report [33], but reached a significance level of $p = 0.03$ (not corrected for multiple comparisons) in a post hoc analysis where the baseline status of many patients had been reclassified [38, 39]. It was also suggested that oral prednisone treatment was associated with an increased risk of recurrent optic neuritis, but not an increased risk of subsequently developing MS [33, 38]. As there was no blinding to methylprednisolone treatment, and as the effect of treatment on MS risk was only observed after reanalysis and reclassification of the initial data, this part of the ONTT must be regarded as a Class III study. Another Class III study (a retrospective natural history study) has suggested that i.v. methylprednisolone treatment (1 g once daily for 3 days) could actually increase the risk of subsequently developing MS [40]. In the latter study, a surprisingly low risk of conversion to MS was, however, observed in the control group of untreated patients and patients treated with oral prednisone.

**Glucocorticoid treatment in MS subgroups**

Whether subgroups of patients with MS relapses may benefit more from glucocorticoid treatment has been addressed in only a few studies. It has been suggested that patients with more severe relapses are more likely to respond to treatment with i.v. methylprednisolone (Class IV evidence) [41]. Another uncontrolled (Class IV) study suggested that patients with high cerebrospinal fluid (CSF) concentrations of myelin basic protein (MBP) are more likely to improve after i.v. methylprednisolone
treatment. This finding was confirmed using 1-week follow-up data in a post hoc analysis of patients included in two randomized, placebo-controlled trials of oral high-dose methylprednisolone treatment. However, the additional benefit of methylprednisolone treatment in patients with high CSF concentrations of MBP was not sustained at follow-up after 8 weeks, while patients who had an active gadolinium-enhanced MRI at baseline appeared to benefit from treatment even at follow-up after 8 weeks (Class III evidence).

Side effects of glucocorticoid treatment

In the placebo-controlled trials serious adverse events were not observed after high-dose methylprednisolone treatment. Did not report the precise frequency of adverse events, but noted that treatment was surprisingly free from serious adverse events. Those most frequently reported were a slight reddening of the face, transient ankle swelling, and a metallic taste in the mouth during infusion. In the Cochrane review it was concluded that the oral administration of methylprednisolone is associated with a higher frequency of side effects (mainly gastrointestinal and psychic disorders), and that oral administration should be avoided for this reason. In the study of Durelli et al., the incidence of elevated mood and insomnia increased during the study from two out of 11 patients (18%) treated with intravenous high-dose methylprednisolone at day 5 to five out of 11 patients (45%) at day 15. In the study of oral high-dose treatment with an oral tapering dose and a total treatment duration of 15 days, disturbed sleep was observed in 65% and slight mood changes in 23%, which is not significantly different from the frequency observed by Durelli and coworkers. Durelli and coworkers (1986) did not report gastrointestinal side effects, but all patients received prophylactic antacid treatment. In the study of oral high-dose methylprednisolone treatment, gastrointestinal side effects (mainly heartburn not requiring symptomatic treatment) were observed in 38% of patients treated with oral methylprednisolone and 8% in the placebo group. The randomized comparisons of i.v. and oral treatment with methylprednisolone at equivalent doses found that the side effects of oral and i.v. methylprednisolone treatment were similar. This is supported by the results of a smaller, non-randomized Class III study comparing treatment with i.v. methylprednisolone and oral prednisone at equivalent doses, which also failed to detect any difference in the side effects of oral and i.v. treatment.

In a review of 240 patients, who had been treated with one or more courses of i.v. methylprednisolone (1 g daily for 5 days followed by 10 days of oral prednisone treatment), minor infections were observed in four patients; one patient had a single seizure within 12 h of treatment, 11 patients were noted to have glucosuria during treatment, five had gastrointestinal symptoms that required antacid or H2 antagonist treatment, three patients had an exacerbation of acne, ankle oedema was recorded in two patients, and one patient was hypertensive during treatment.

Severe side effects of methylprednisolone treatment are rare, but psychosis, acute pancreatitis, and anaphylactoid reactions to i.v. treatment have been reported. Short-term methylprednisolone treatment in patients with MS appears to be safe in terms of long-term effects on bone mineralization, but pulsed methylprednisolone treatment has short-term effects on bone metabolism. Short-term methylprednisolone treatment may not be negligible.

Other treatments

A single Class I crossover study of 22 patients with severe relapses of inflammatory demyelination (including 12 with MS) who were refractory to treatment with high-dose methylprednisolone suggested a beneficial effect of treatment with plasma exchange. In this study there was ‘moderate’ or ‘marked’ improvement during plasma exchange treatment in eight out of 19 patients (42%), whereas such improvement was observed only after one out of 17 courses (6%) of sham treatment (p = 0.01). Open (Class IV) studies have also reported an effect of plasma exchange in patients with acute optic neuritis who had not improved after high-dose i.v. methylprednisolone treatment. One study found that an effect of plasma exchange that was sustained after 6
months was more likely when treatment was initiated early and in patients who had shown improvement already at hospital discharge [55].

Intravenous immunoglobulin (IVIg) treatment is widely used in a variety of neurological diseases. A single Class IV study of intravenous IVIg treatment in relapses of MS suggested that as many as 68% of patients improved within 24 h of treatment [56]. Two studies have investigated if IVIg treatment as add-on to therapy with high-dose i.v. methylprednisolone is superior to add-on placebo treatment [57, 58]. Both studies were negative on primary and secondary end-points.

A phase III study of IVIg treatment reported marked improvement in 23 patients with severe visual impairment after methylprednisolone treatment of optic neuritis, whereas there was no improvement in a control group comprising 24 patients treated with methylprednisolone only [59]. However, in this study spontaneous recovery in the control group was surprisingly poor, and a randomized Class I trial of treatment with IVIg or placebo in 68 patients with acute optic neuritis failed to detect any treatment effect [60].

Whereas treatment with natalizumab lowers the frequency of relapses in MS, natalizumab was not efficacious in the treatment of relapses in a randomized, placebo-controlled Class I study of 180 patients with an MS relapse [61].

A single Class II study compared the effect of multidisciplinary rehabilitation with the effect of ‘standard therapy’ in a randomized clinical trial design, where both treatment arms received i.v. methylprednisolone treatment. The study suggested that a multidisciplinary team rehabilitation programme results in better functional recovery after 3 months than does treatment with i.v. methylprednisolone in a ‘standard’ setting [62].

**Treatment of relapses during pregnancy**

There are no specific studies on relapse treatment in pregnant patients with MS, but short-term treatment with glucocorticoids is generally considered safe in pregnant women, and treatment may be considered in patients with a relapse of sufficient severity to warrant treatment, although treatment during the first trimester should probably be avoided (Class IV evidence [63]).

### Recommendations

There is consistent evidence from several Class I studies and meta-analyses for a beneficial effect of glucocorticoid treatment in relapses of MS. Hence, treatment with intravenous or oral methylprednisolone in a dose of at least 500 mg daily for 5 days should be considered for treatment of relapses (Level A). Treatment with i.v. methylprednisolone (1 g once daily for 3 days with an oral tapering dose) may be considered for treatment of acute optic neuritis (Level B). Treatment with i.v. methylprednisolone (1 g once daily for 3 days) should be considered as an alternative treatment (GPP, [8]).

There is no evidence of major differences in the efficacy of methylprednisolone treatment given i.v. or orally in terms of clinical efficacy or side effects, but prolonged oral treatment may possibly be associated with a higher prevalence of side effects. Furthermore, due to the low number of patients included in the available clinical trials, some efficacy differences between the i.v. and oral route of administration cannot be excluded. The optimal dosage, the specific glucocorticoid to use, and whether to use a taper after initial pulse therapy, has not been adequately addressed in randomized controlled trials. This implies a need for new randomized studies assessing risk/benefit ratios and adverse effects of specific glucocorticoids, dose, and route of administration for treatment of MS relapses.

There is insufficient data to clearly define patient subgroups who are more likely to respond to methylprednisolone treatment, but treatment may be more efficacious in patients with clinical, MRI, or CSF evidence indicating higher disease activity (Level C recommendation). Home versus outpatient administration of i.v. steroids was evaluated in one clinical trial [64], and in one large French survey of home-based treatment of MS relapses with i.v. methylprednisolone [65]. The results of both studies indicate that treatment with i.v. steroids can be effectively and safely administered at home. Consideration may, however, sometimes be given to administering the first course of methylprednisolone as an inpatient (GPP).

In patients who fail to respond to therapy with methylprednisolone in the dose range used in the randomized, placebo-controlled trials [10, 11, 13, 15], treatment with higher doses (up to 2 g daily for 5 days) should be considered (Level C recommendation [8]).
There is insufficient data to support the use of IVIg therapy as monotherapy for relapses of MS. Treatment with IVIg as an add-on to treatment of MS relapses with methylprednisolone or as monotherapy for acute optic neuritis is not efficacious (Level A recommendation). Neither is natalizumab as monotherapy efficacious in MS relapses.

Patients with inflammatory demyelination, including patients with MS, who have not responded to treatment with methylprednisolone may benefit from plasma exchange treatment, but only about one-third of treated patients are likely to respond. This treatment regimen should probably be restricted to a subgroup of patients with severe relapses (Level B recommendation). A randomized controlled study specifically addressing the effect of plasma exchange and IVIg treatment in patients with severe relapses (Level B recommendation). A randomized controlled study specifically addressing the effect of plasma exchange and IVIg treatment in patients with severe relapses of MS not responding to methylprednisolone treatment would be desirable.

A more intense, interdisciplinary rehabilitation programme should be considered after treatment with i.v. methylprednisolone as evidence from a single trial suggests that this probably further improves recovery (Level B recommendation).

Conflicts of interest
Authors of this chapter have received the following: honoraria for lecturing, serving on advisory councils or trial steering committees; covering of travel expenses for attending meetings; or research grants from Almirall, Bayer Schering Pharma, Biogen Idec, EMD, Genentech, GenMab, Genzyme, Lundbeck, Merck Serono, Novartis, Novo Nordisk, Sanofi-aventis or Teva.

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