Infectious Mononucleosis and Corticosteroids

Management Practices and Outcomes

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Objective: Although many studies have examined the effects of systemic corticosteroid therapy (SCT) on the clinical course of infectious mononucleosis (IM), few have evaluated the influence of these studies on treatment patterns and outcomes. The purpose of this study was to review current therapeutic strategies and outcomes in uncomplicated and complicated IM.

Design: Retrospective case series.

Setting: Tertiary care center.

Patients: We identified 206 immunocompetent patients with IM diagnosed during the previous 5 years. Patient information, including age, sex, history and physical findings at presentation, pertinent laboratory data, management practices, and treatment outcomes, were analyzed.

Interventions: Systemic corticosteroid therapy was used in 44.7% of patients. Evaluation of treatment indications for SCT revealed that 8.0% of the study population qualified by traditional criteria for the use of corticosteroids; 92.0% of patients received SCT for other indications. Factors associated with the observed increase in corticosteroid use included a history of repeat visits, inpatient admission, and otolaryngology consultation.

Main Outcome Measures: Diagnosis was made on the basis of a positive heterophil antibody test (monospot test) with appropriate clinical findings (97.5% of patients) or by the presence of lymphocytosis with appropriate clinical findings (2.4% of patients).

Results: Systemic corticosteroid therapy was not positively associated with fever, decreased oral intake, tonsillar hypertrophy, or duration of symptoms. No significant differences in incidence of disease complications, rates of hospital admission, or length of hospital stay were noted between the steroid and nonsteroid treatment groups.

Conclusions: Despite consistent and uniform acceptance in the medical literature that SCT in the setting of IM should be reserved for patients with impending airway obstruction, corticosteroids continue to be used on a much broader scale at this tertiary care institution. This observation suggests that clinicians see value in SCT for treatment of IM beyond the classically accepted reasons. Moreover, despite previous reports of possible adverse consequences of SCT in IM, our review failed to demonstrate any such trend.

1998 through March 2003 were reviewed. A diagnosis was made on the basis of positive heterophile antibody test results (monospot test) or elevated Epstein-Barr virus (EBV) IgM levels with appropriate clinical findings or by the presence of lymphocytosis with appropriate clinical findings. Appropriate clinical findings included at least 3 of the following: fever, pharyngitis, cervical lymphadenopathy, tonsillar hypertrophy or exudate, and hepatosplenomegaly. Patients with chronic immunocompromise and those with a positive monospot test but no other evidence of IM were excluded. Details of patient findings at presentation, diagnosis, treatment, and outcome were analyzed. Statistical analysis was performed with the χ² analysis.

RESULTS

Two hundred six patients met the criteria for a diagnosis of IM. The group with positive antibody tests represented 97.5% (201/206) of the patients, whereas 2.4% (5/206) of the patients had negative antibody tests but met the diagnostic criteria on the basis of lymphocytosis and clinical findings. The adolescent and young adult population (aged 13-25) represented 80.6% (166/206) of the patients, and those younger than 13 and older than 25 represented much smaller groups at 13.1% (27/206) and 6.3% (13/206), respectively. Sex was fairly evenly split, with 99 male patients (48.1%) and 107 female patients (51.9%).

The history at presentation varied, but most commonly included sore throat (79.1%), history of a previous visit (67.0%), fever (63.6%), and dysphagia (58.7%). Average duration of symptoms at presentation was 9.7 days. The most common physical finding was cervical lymphadenopathy (78.8%), followed by tonsillar hypertrophy (70.4%), exudative tonsillitis (60.4%), fever (30.6%), and hepatosplenomegaly (27.1%). Laboratory evaluation found that 195 patients (94.7%) had positive monospot tests, whereas 147 patients (71.4%) had either absolute lymphocytosis or atypical lymphocytosis.

The 6 patients (2.9%) in whom no monospot test was performed had elevated EBV IgM titers. Twelve (9.4%) of 128 patients tested positive by “rapid strep” test for group A β-hemolytic streptococcus.

Nearly 45% (92 of 206 [44.7%]) of all patients with acute IM received SCT at some time during their illness. Of the 137 patients who had been seen on a separate occasion by their primary care physician (PCP), 30 (21.9%) received oral SCT at that initial visit. All but 4 of these patients (86.7%) continued to receive SCT after evaluation in our emergency department (ED). The dosages and indications for use in these 4 patients were not available, and they were not included in further analysis of patients who received SCT. Including the additional 62 patients in whom SCT was initiated after evaluation in our ED, the overall SCT treatment rate at our hospital was 42.7% (88 of 206 patients). Specific steroids used, dosages, routes of administration, and duration of treatment differed dramatically among the population studied. In general, patients who were not admitted received 1 intravenous dose of dexamethasone sodium phosphate, 0.5 mg/kg, with or without a short course of oral steroids at discharge. Inpatients generally received dexamethasone, 0.5 mg/kg, or an equivalent dose of methylprednisolone acetate, every 8 hours for at least 24 to 48 hours.

Most patients given SCT by their PCP continued taking steroids after presentation to the ED. However, similar consistency was not present with antibiotic use. Of the 137 patients evaluated by their PCP on an occasion before their ED presentation, 63 (46.0%) were taking antibiotics at that time. While treatment would have been considered to have failed in all of these patients because of their subsequent ED presentation, fewer than half (28 of 63 [44.4%]) of this group were thought to have disease warranting antibiotic therapy when seen in the ED. The overall antibiotic use rate by the ED or hospital was 35.4% (73/206). Of the 206 patients included in the study, 108 (52.4%) received antibiotic therapy at some time during their illness. As would be expected, all of the patients who tested positive for group A β-hemolytic streptococcus were in this group. However, after subtracting the 27 patients who were treated either for positive cultures or other infectious indications (eg, pertonsillar abscess, pneumonia), a significant number of patients (81 of 179 [45%]) still received antibiotic therapy during the course of their illness. Although we found no consistent justification for the use of antibiotics, one recurring “indication” was the concern for bacterial superinfection with the use of steroids without antibiotics.

Sixty-four of 206 patients (31.1%) required inpatient admission. Indications for admission included severe and persistent symptoms, dehydration, hyperpyrexia, concern for airway obstruction, and other systemic complications. Average hospital length of stay was 4.6 days. Otolaryngology consultation was obtained in 37 (18.0%) of 206 patients. The reported disease complication rate was 5.3% (11/206) and included peritonsillar abscess in 4 patients, splenic rupture in 2, pneumonia in 2, and idiopathic thrombocytopenic purpura, empyema, and mediastinal abcess in 1 patient each. Surgical intervention was required in 15 patients (7.3%) and included tonsillectomy in 7 patients, drainage of peritonsillar abscess in 4, splenectomy in 2, and thoracotomy in 2.

Examination of the reported clinical indications for SCT use showed that “airway concern” was cited in just 7 of 88 (8.0%) patients, and idiopathic thrombocytopenic purpura in 1 patient. For the remaining 81 patients (92.0%) the treatment indications listed were poor oral intake or severe dysphagia or odynophagia, persistent symptoms, repeat visits, or reasons not elucidated on the medical record (Figure).

Patient groups with and without SCT were compared for sex, age, disease severity, history of a previous visit, hospital admission rates, otolaryngology consultation, and complications of IM. No positive correlation between SCT and sex, age, or any other clinical characteristics used to diagnose IM (eg, fever, duration of symptoms, tonsillar hypertrophy) was identified.

However, analysis of SCT based on history of a previous visit revealed that patients seen by their PCP on an occasion before ED presentation were more likely to receive steroids than were those seen for the first time. Similarly, patients admitted to the hospital were nearly twice as likely to receive steroids as those managed as outpatients (Table 1). These patients were most likely those with the most severe clinical symptoms.

Patients seen by otolaryngologists were also more likely to receive SCT. Indeed, 83.8% (31/37) of patients seen...
by an otolaryngologist during their illness received steroids, whereas only 33.7% (57/169) of patients not seen by an otolaryngologist received steroids (P .001; Table 1). As might be expected, analysis of the patients seen by otolaryngologists revealed increased rates of dehydration, dysphagia or odynophagia, tonsillar exudate, and tonsillar hypertrophy. However, the increased use of SCT by otolaryngologists was not supported by an increased rate of airway obstruction in these patients. Concern for possible airway compromise was mentioned in only 3 (8.1%) of 37 patients.

In an effort to compare clinical course and outcomes between SCT and non-SCT groups, rates of hospital admission, length of stay, and incidence of complications were compared, and no significant differences were identified (Table 2). More patients treated with SCT before presentation to our institution (patients prescribed SCT by their PCP) were eventually admitted than were those not prescribed SCT. Although this difference is not statistically significant (P = .26), the apparent higher rate of admission for patients with a history of SCT is probably explained by the fact that this group of patients generally had slightly higher rates of dehydration, tonsillar hypertrophy, and tonsillar exudate.

As for the question of steroids and infectious complications, SCT use has been implicated previously in the development of infectious complications of IM, although little evidence exists to support this claim. Examination of justifications given by practitioners in this study for the use of prophylactic antibiotic therapy suggests persistent concern in this regard. Indeed, the most commonly cited justification for antibiotic therapy when no clear indication existed was concern about possible bacterial superinfection with the use of SCT. However, as shown in Table 2, no significant difference in complication rates between SCT and non-SCT groups was identified. It is interesting, however, that 4 of the 8 infectious complications of IM (3 peritonsillar abscesses and 1 mediastinal abscess) developed in the relatively small group of 17 patients who received SCT but no antibiotics from their PCP at initial presentation. Of the remaining complications, none occurred in the group treated by their PCP initially with SCT and antibiotics. Femur head necrosis, a rare but previously described complication of short-term SCT, was not found in any patient during or after the study.

Although IM is usually a self-limited illness, clinicians continue to search for ways to decrease the severity and duration of the symptoms. Corticosteroids have long been considered a potentially promising solution to this problem. Empirical reports of therapeutic benefit abound, and many studies have attempted to either corroborate or dispute these claims. Early studies by Prout and Dalrymple, Bender, and Klein et al randomly assigned large populations of college students with IM to receive SCT or placebo with or without antibiotics. These studies generally concluded that patients given SCT had decreased duration of fever and shorter duration of symptoms. Although more recent studies have noted similar results, studies by Collins et al and most recently by Tynell et al found no improvement in duration of illness, sore throat, weight loss, or absence from school or work.

While controversy surrounds the issue of steroids and uncomplicated IM, clinicians universally agree that SCT is indicated in the case of airway obstruction secondary to IM. Several authors have described their success in averting emergency surgical procedures (eg, tonsillectomy, tracheostomy) with the use of SCT and intravenous fluids in patients with impending airway obstruction.

Figure. The overwhelming majority of patients given corticosteroids received them for indications other than the classically accepted airway concerns and idiopathic thrombocytopenic purpura (ITP).

Table 1. Percentage of Patients Receiving Systemic Corticosteroid Therapy*

<table>
<thead>
<tr>
<th>Patient History</th>
<th>SCT</th>
</tr>
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<tbody>
<tr>
<td>None</td>
<td>17.0 (15/88)</td>
</tr>
<tr>
<td>Previous</td>
<td>83.0 (73/88)</td>
</tr>
<tr>
<td>Treatment</td>
<td>33.1 (47/142)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>64.1 (41/64)</td>
</tr>
<tr>
<td>Consultation</td>
<td>83.8 (31/37)</td>
</tr>
<tr>
<td>None</td>
<td>33.7 (57/169)</td>
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</tbody>
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Table 2. Outcome Comparison by Treatment Method

<table>
<thead>
<tr>
<th>Outcome</th>
<th>SCT</th>
<th>Non-SCT</th>
<th>P*</th>
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</thead>
<tbody>
<tr>
<td>Inpatient admission, % (n)</td>
<td>40.0 (12/30)</td>
<td>29.0 (31/107)</td>
<td>.26</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>2.4</td>
<td>3.1</td>
<td>.45</td>
</tr>
<tr>
<td>Complication rate, % (n)</td>
<td>4.3 (4/92)</td>
<td>2.6 (3/114)</td>
<td>.56</td>
</tr>
</tbody>
</table>

*Abbreviation: SCT, systemic corticosteroid therapy.

*No significant differences in admission rates, length of hospital stay, or complication rates were noted between SCT and non-SCT groups.
The question of SCT use in IM is not just relevant because of the potential for improvement of symptoms. Transient depression of non–EBV-specific cell-mediated immune functions early in the course of IM is well documented.\(^7\)\(^,\)\(^12\) In addition, corticosteroids impair cell-mediated immunity by decreasing the numbers and sensitivity of circulating lymphocytes and monocytes.\(^8\)\(^,\)\(^19\) In studying the immune response in patients with IM, Fleisher et al\(^6\) noted delayed appearance of EBV-associated nuclear antigen in patients given SCT. Although no studies have shown an increase in IM-associated complications with SCT, experts have frequently warned against “possible adverse consequences” of steroid use in the setting of IM.\(^6\)\(^,\)\(^9\)\(^,\)\(^10\) In addition, reports of infectious complications associated with IM frequently implicate corticosteroids as possible contributing factors.\(^20\)\(^-\)\(^22\) However, a review of these case reports revealed no consistent patterns of corticosteroid use.\(^20\)\(^-\)\(^29\) Furthermore, the aforementioned complication of SCT, femur head necrosis, has never been described after SCT for IM.

Despite all of the suspicions about SCT, no differences in complication rates have been reported. Our similar complication rate between treated and nontreated groups agrees with previous findings. However, it must be remembered that, despite the apparent similarity in complication rates, dosages, duration of SCT, and the use of concurrent antibiotic therapy differed significantly among the treated population, making comparison more difficult. Also, the observation of a seemingly disproportionate number of infectious complications (4/8) developed in the subset of patients treated initially with SCT without antibiotic therapy raises questions about whether there is justification for the concern of suppressed immunity and subsequent bacterial superinfection so often cited by practitioners.

Major references and review articles consistently recommend against the use of SCT in most patients with IM.\(^7\)\(^,\)\(^10\)\(^-\)\(^12\)\(^,\)\(^30\) However, our study suggests that SCT may be used much more broadly and routinely than might otherwise be expected. Reasons for this discrepancy and the merits of this practice are probably difficult to describe. One explanation may be that patients demand results and clinicians prescribe in response to demand. The significant use of antibiotics in the setting of negative streptococcal cultures, as in this study, and the increased use of SCT when patients returned with persistent symptoms support this hypothesis.

Another contributing factor may be that treatment patterns are based partially on evidence-based medicine, but also to a large extent on each practitioner’s personal training, clinical judgment, and experience. This was highlighted in an editorial by Disney,\(^31\) who empirically noted dramatic differences in symptom relief in his patients who were treated with corticosteroids. He asserted, as have many other clinicians, that he would continue to offer his patients what was, to him, an obviously beneficial treatment despite what the literature might say.

Finally, the apparent increased use of SCT by otolaryngologists may be partially accounted for by their heightened awareness of serious infectious and airway complications of any type of pharyngitis. This theory is supported in that most patients seen by otolaryngologists had significant tonsillar hypertrophy.

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REFERENCES