Infectious Mononucleosis and Corticosteroids

Management Practices and Outcomes

Scott K. Thompson, MD; Timothy D. Doerr, MD; Arthur S. Hengerer, MD

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.

A diagnosis was made on the basis of positive heterophil 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

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, peritonsillar 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 abscess 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.
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.\textsuperscript{7,12} In addition, corticosteroids impair cell-mediated immunity by decreasing the numbers and sensitivity of circulating lymphocytes and monocytes.\textsuperscript{19} In studying the immune response in patients with IM, Fleisher et al\textsuperscript{8} 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.\textsuperscript{5,9,10} In addition, reports of infectious complications associated with IM frequently implicate corticosteroids as possible contributing factors.\textsuperscript{20-22} However, a review of these case reports revealed no consistent patterns of corticosteroid use.\textsuperscript{20,22} 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 that 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.\textsuperscript{7,10-12,30} However, our study suggests that SCT may be used more broadly and routinely than might otherwise be expected. Reasons for this discrepancy and the merit 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,\textsuperscript{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.

CONCLUSIONS

The treatment of IM has been and will continue to be a subject of controversy and debate. While recommendations and clinical studies dealing with IM are abundant, no recent studies have examined management practices and related outcomes. Our study corroborates previous assessments of typical symptoms, presentation, findings, and overall outcomes of IM.\textsuperscript{5,9,10} In addition, we assert that, despite recommendations to the contrary, much more liberal use of corticosteroids is the norm at this institution. Factors associated with corticosteroid use include a history of more than 1 visit, inpatient admission, and otolaryngologic consultation. No apparent increases or decreases in the incidence of complications, rates of admission, or length of hospital stay were noted with treatment. However, prospective randomized trials are necessary to definitively assess these findings. Nevertheless, published trials are just one factor contributing to the complex and sometimes difficult task of managing illness. The art of medicine will always be a balance between objective evidence and the experience and wisdom of the practitioner.

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Correspondence: Scott K. Thompson, MD, Department of Otolaryngology–Head and Neck Surgery, University of Rochester Medical Center, 601 Elmwood Ave, Campus Box 629, Rochester, NY 14642 (Scott_Thompson@urmc.rochester.edu).

REFERENCES


