Erythema Multiforme and Stevens-Johnson Syndrome*
Descriptive and Therapeutic Controversy
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Diagnosis and particularly the management of erythema multiforme and Stevens-Johnson syndrome are controversial in medical textbooks and thus in individual cases. In these diseases, fatalities may result from various causes, including secondary infection or visceral organ damage to lung, liver, or kidneys. We present a series of 13 cases managed by one group of physicians which demonstrates the controversy in certain cases, and we review the controversy in the medical literature. Corticosteroid therapy used in this series was considered beneficial in every case by the managing physician and lifesaving in some cases. There were no fatalities in this series. Although the summation may be considered as our opinion only, the frequently suggested “controlled trial of corticosteroid therapy” can probably never be done for ethical reasons, and series such as this will have to establish the standard of therapy.

(Chest 1990; 98:331-36)

EI = Allergy-Immunology

The diagnosis and management of erythema multiforme and Stevens-Johnson syndrome are complex and controversial. Problems in diagnosis and interpretation of published reports result from the descriptive variations of these two clinical problems and of toxic epidermal necrolysis or Lyell’s syndrome in various texts. The therapeutic problem we wish to present is that, in our opinion, the use of corticosteroids, which is often described as controversial, is indicated and may be essential to survival in severe cases. Further, the managing physician in such severe cases may be in a difficult position if several complex issues are involved, as follows: a managing physician may believe that corticosteroids are essential for management and possibly for survival, and a consultant may clearly oppose the use of corticosteroids. This controversy may be seriously complicated by a potential litigious outcome when the case may appear to be a drug reaction, when there is a risk of permanent cosmetic or organ damage or both, or particularly when both a drug reaction is suspected and permanent cosmetic or organ damage occurs; for example, pulmonary involvement has been reported in three publications,1-3 with pulmonary involvement in up to 31 percent of the cases in one series.3

As we will review, the terminology regarding erythema multiforme and Stevens-Johnson syndrome is variable. For this report, we shall define these clinical problems as follows: erythema multiforme is an erythematous maculopapular cutaneous eruption of variable form, as its name implies. Classically, there is a target lesion, with a predilection for the extremities. Erythema multiforme may occur as a mild, self-limited cutaneous manifestation or grade into progressively more serious cutaneous lesions with vesicular or bullous lesions. Mucosal involvement may occur, involving selected or all mucosal surfaces. Visceral organ involvement, such as pulmonary and renal involvement may occur, and general toxic effects in the patient may be serious. When erythema multiforme grades into a more serious clinical state, the terms, erythema multiforme bullous or Stevens-Johnson syndrome, are used. The overlap with the term, toxic epidermal necrolysis, is further confusing. We shall consider Stevens-Johnson syndrome as the severe manifestation of erythema multiforme with mucosal involvement, with or without bullous lesions. Toxic epidermal necrolysis is considered the most severe clinical extreme of erythema multiforme or Stevens-Johnson syndrome. We recognize that other experts may have different classifications.

We will present a case which typifies the problem and a selective review of specialty textbooks which, we believe, demonstrate the origin of the controversy. We will also present our series of 13 consecutive cases, outlining our therapeutic approach and the outcome and opinions of the physicians involved in therapeutic management.

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MATERIALS AND METHODS

Patients
All patients in this series were managed totally or as consultants by one or more of the authors of this report. Data were collected using a standardized form completed by the authors involved in a patient's care. For the analysis of the course of patient 1 (presented as a case report), data were collected in the following manner: after the initial diagnosis, initiation of prednisone therapy, and improvement of clinical status, it became apparent that the use of prednisone was controversial and in conflict with the written opinion of a consulting physician. Because of the concern for the patient's welfare and the possible litigious issues involved, six physicians of the AI service were asked to evaluate the patient and to consider and advise on prednisone therapy. Subsequently, these six physicians were given a blank graph and asked to grade the patient's lesions on a scale of 1 to 5 in comparison with their initial observation, which occurred on days 1 or 2 after our service was consulted. The severity was graded on the basis of the extent of lesions, the severity of lesions, and the development of new lesions. Grade 5 denoted the most severe clinical symptoms. The grade of severity assessed by different physicians on any particular day was averaged. All physicians did not see the patient daily, and the results were tabulated and averaged based on this severity score index.

CASE REPORT
A 53-year-old white woman with Graves' disease (case 1) was seen in consultation for dermatitis consisting of erythematous raised lesions of variable size, generally occurring over her extremities, but also over the trunk and face. The nose was severely involved. A very severe conjunctivitis was present bilaterally. The other mucosal surfaces were normal.

The medical history of the patient was that she was in generally good health except for Graves' disease, for which she was first treated with propylthiouracil several months prior to admission. In the weeks prior to admission, propylthiouracil had been used erratically by the patient. Seven days prior to admission, she had had the onset of fever (39.4°C [103°F]) and systemic symptoms of fatigue and myalgia. At the time of admission, the patient had a temperature of 38.3°C (101°F) and agranulocytosis with an absolute neutrophil count of 36/cu mm. She was treated with piperacillin and gentamicin and subsequently with vancomycin. On the fourth day of hospitalization, a macular eruption occurred on the skin. Because of a possible drug reaction to piperacillin, therapy with this drug was discontinued on the fifth day of hospitalization, but the cutaneous eruption progressed. It was the opinion of the AI service that the patient had Stevens-Johnson syndrome because of the nature of the cutaneous lesions and mucosal involvement of the conjunctiva. Further, the AI consultants advised that therapy with prednisone at 80 mg be initiated immediately because of the severity of the patient's illness and the general toxic effects. Unknown to physicians, the patient refused the prednisone. The day when this occurred is day 1 of Figure 1, the first day of allergy consultation, which was the tenth day of hospitalization. By the next morning the patient appeared worse because of general toxic effects and the severity of the cutaneous lesions. She refused intravenous steroids but accepted the immediate administration of 80 mg of prednisone orally. Figure 1 illustrates the general course of the severity of the illness based on the evaluation of the AI consultants as described in the methods section. The dose of prednisone that the patient received in relation to the severity of the manifestations of the patient's disease is shown. The arrows denote the days when a consultant verbally (v) or in writing (w) criticized the therapeutic use of corticosteroids and objected to the use of the term, Stevens-Johnson syndrome. Because of the severity of the patient's disease, some confusion on the part of the patient due to general toxic effects, the anger of the patient's family, and possible litigious action by the patient's family, the entire AI team consulted on the patient. High-dose therapy with prednisone (80 mg) was used initially. The dosage was then relatively rapidly reduced to 40 mg/day after stabilization and improvement of the Stevens-Johnson syndrome. Further improvement on this dosage of prednisone did not occur, and four days later, there was a significant increase in new lesions. The dosage of prednisone was increased, and the manifestations of Stevens-Johnson syndrome subsided. The patient was discharged first on therapy with 40 mg of prednisone daily and subsequently was managed on a tapering course of alternate-day therapy with prednisone. There is no residual cutaneous scarring or end-organ damage. Complete recovery from the agranulocytosis was also observed.

Comment

This patient was a complex diagnostic and management problem, with initial concerns being the question of infection, drug reaction, or other unknown problems. Controversy occurred over nomenclature (erythema multiforme vs Stevens-Johnson syndrome) and the use of prednisone. The AI physicians believed that therapy with prednisone would control and reverse the lesions and possibly prevent organ damage and permanent cosmetic changes, particularly of the nose, which was seriously involved. During hospitalization, the dosage of prednisone was more rapidly decreased than we have done in other cases because of hostile comments by a consultant and the patient's and family's concern. The decline in the dosage of prednisone was associated with an exacerbation, which subsequently subsided with the increased use of prednisone. Although the course of the disease process and its relation to prednisone therapy described herein and shown in Figure 1 may be coincidental, it is the opinion of the AI staff on the basis of other experience with this syndrome that prednisone was necessary and may have been lifesaving.

RESULTS

Analysis of Cases

All cases of patients with the diagnosis of Stevens-Johnson syndrome seen by the authors are shown in Tables 1 and 2. Most of the cases were seen by more
Table 1—Characteristics of Cases of Erythema Multiforme or Stevens-Johnson Syndrome Treated with Corticosteroids

<table>
<thead>
<tr>
<th>Patient, Sex, Age (yr)</th>
<th>Percent Skin Involvement</th>
<th>Bullous Lesions</th>
<th>Mucosal Lesions*</th>
<th>Visceral Involvement</th>
<th>Drug Reaction or Infection Suspected: Drug or Organism</th>
<th>Days Prior to Onset of Corticosteroids</th>
<th>Initial Corticosteroid Dose/Day†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, F, 53</td>
<td>60</td>
<td>E</td>
<td>—</td>
<td>—</td>
<td>Propylthiouracil; piperacillin; Cephalosporin; sulfa</td>
<td>7</td>
<td>5 P; 80 mg</td>
</tr>
<tr>
<td>2, F, 62</td>
<td>&gt;90</td>
<td>O; R</td>
<td>Kidney</td>
<td>—</td>
<td>Penicillin; diphenylhydantoin</td>
<td>17</td>
<td>H; 1 g</td>
</tr>
<tr>
<td>3, F, 20</td>
<td>&gt;90</td>
<td>O</td>
<td>—</td>
<td>Kidney</td>
<td>Mexiletine</td>
<td>1</td>
<td>H; 1 g</td>
</tr>
<tr>
<td>4, M, 72</td>
<td>70</td>
<td>O; E</td>
<td>Kidney</td>
<td>—</td>
<td>Diphenylhydantoin; phenobarbital</td>
<td>8</td>
<td>P; 100 mg</td>
</tr>
<tr>
<td>5, M, 42</td>
<td>70</td>
<td>O; E</td>
<td>Liver</td>
<td>—</td>
<td>Doxycycline</td>
<td>4</td>
<td>H; 1.3 g</td>
</tr>
<tr>
<td>6, F, 58</td>
<td>50</td>
<td>O; E</td>
<td>—</td>
<td>Kidney</td>
<td>Penicillin</td>
<td>1</td>
<td>H; 1 g</td>
</tr>
<tr>
<td>7, F, 26</td>
<td>100</td>
<td>E; N; O; V</td>
<td>Liver</td>
<td>—</td>
<td>No drug suspected; viral etiology; suspected</td>
<td>3</td>
<td>H; 100 mg</td>
</tr>
<tr>
<td>8, F, 38</td>
<td>80</td>
<td>E; O; V</td>
<td>Pneumonia; liver; kidney</td>
<td></td>
<td>Amoxicillin</td>
<td>5</td>
<td>H; 120 mg</td>
</tr>
<tr>
<td>9, F, 39</td>
<td>100</td>
<td>E; O; V</td>
<td>—</td>
<td>—</td>
<td>Amoxicillin</td>
<td>5</td>
<td>P; 20 mg</td>
</tr>
<tr>
<td>10, M, 2.5</td>
<td>80</td>
<td>E; O; U</td>
<td>Kidney</td>
<td>—</td>
<td>Amoxicillin</td>
<td>5</td>
<td>H; 80 mg</td>
</tr>
<tr>
<td>11, M, 1</td>
<td>70</td>
<td>O</td>
<td>Kidney</td>
<td>—</td>
<td>Amoxicillin</td>
<td>5</td>
<td>P; 15 mg</td>
</tr>
<tr>
<td>12, M, 31</td>
<td>80</td>
<td>E</td>
<td>—</td>
<td>—</td>
<td>Megestrol acetate (Megace); qd × 5 days prior to onset</td>
<td>3</td>
<td>H; 1 g</td>
</tr>
<tr>
<td>13, M, 58</td>
<td>80</td>
<td>E; O</td>
<td>—</td>
<td>—</td>
<td>Diphenylhydantoin</td>
<td>5</td>
<td>H; 800 mg</td>
</tr>
</tbody>
</table>

*E, Eye; O, oral; R, rectal; N, nose; V, vaginal; and U, urethral.
†P, Prednisone; and H, hydrocortisone.

than one of the authors, with concurrence of opinion in both diagnosis and therapy.

Case 1 is the case report described in detail and shown in Figure 1. Case 7 was previously reported.4

Recommendations Regarding Corticosteroids

The recommendations of commonly used textbooks of pediatrics, internal medicine, and dermatology are summarized in Table 3.5-14 It is apparent that specific guidance on the use of corticosteroids is variable and will remain variable in the absence of a controlled trial, which we do not believe can be accomplished ethically.

Discussion

Although cutaneous lesions are usually the presenting symptom in these syndromes, visceral organ involvement may be present, severe, and potentially life-threatening. Pulmonary involvement occurs in some cases,1-3 and thus pulmonologists and critical care physicians may be consultants or managing physicians.

We report cases in which the coauthors all were involved in the patients' management; all physicians believed corticosteroids benefitted these patients and may have been lifesaving in several cases. We fully recognize that these patients may be considered a group of anecdotal cases, that no large controlled study has been done on the use of corticosteroids, and that patients with mild erythema multiforme may recover without corticosteroid therapy.

A survey of textbooks of pediatrics, internal medicine, and dermatology was conducted, and our interpretation of the recommendations are in quotations, as we could not include the entire relevant text (Table 3). We believe that many authors support the use of corticosteroids in patients with erythema multiforme or Stevens-Johnson syndrome and that the managing physician can and should use these agents if the severity of the disease or its progression justifies this therapy. Of importance in this series of patients is that managing physicians believed corticosteroids were not only essential for management but possibly essential for survival in several cases. Further, there were no adverse effects of corticosteroid use in any case reported herein, with the possible exception of the development of herpetic esophagitis in a patient who was immunocompromised with AIDS, and therefore at increased risk for developing this infection without corticosteroids.

Several authors comment on the need for controlled trials, a laudable goal; however, the problem is that we would not have considered it ethical to withhold corticosteroids in any of these patients presented herein, in order for them to participate in a controlled trial.
The etiology of erythema multiforme or Stevens-Johnson syndrome has been attributed to viral or other infections or drug reactions, or both. As noted in Table 1, a drug reaction was suggested in all cases except one; however, the antibiotics may have been given as therapy for symptoms of a presumed infection which were actually the initial symptoms of the erythema multiforme or Stevens-Johnson syndrome; however, therapy with suspected drugs, even though remotely correlated, must be terminated and permanently avoided. Drug challenges with presumptive drug allergens in patients with a history of erythema multiforme are of extreme risk and can be considered only where the repeat administration of the drug in question is essential for survival.

In the preparation of this report and in the clinical care of patients with erythema multiforme or Stevens-Johnson syndrome, it was apparent that the report of Rasmussen was used as a basis for rejection of the use of corticosteroids as therapy for Stevens-Johnson syndrome. The report of Rasmussen appears to be a retrospective review of records which may have been selective of the most severe cases. As authors of this current report, in which every case was seen or managed by one or more of the coauthors, we believe that this presentation may benefit other patients and the managing physicians. The problems and suggestions for management are summarized in the following tabulation:

Problems
1. Early recognition is difficult, and initial impressions may vary from infection to contact dermatitis to allergic drug reactions. Infection may be present and may be the etiology.
2. Drug reaction may not be suspected sufficiently early so that the drug is not discontinued early enough, particularly in relation to sulfa drugs and phenytoin.

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Table 2—Outcome of Patients in Table 1 Treated with Corticosteroids

<table>
<thead>
<tr>
<th>Patient</th>
<th>Assessed Effect of Corticosteroids</th>
<th>Controversial Issues*</th>
<th>Outcome of Stevens-Johnson</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Improvement of lesion</td>
<td>Consultant advised against CS</td>
<td>Recovery</td>
<td>Potential litigation (see case report and Fig 1)</td>
</tr>
<tr>
<td>2</td>
<td>Dramatic reversal of disease; patient had been moribund</td>
<td>Patient untreated with CS for 17 days; other physicians thought CS dose excessive</td>
<td>Recovery</td>
<td>Patient comatose and moribund prior to use of CS; dramatic reversal of disease with CS</td>
</tr>
<tr>
<td>3</td>
<td>Reversal of lesions</td>
<td>None</td>
<td>Recovery</td>
<td>Severity and extent of cutaneous and mucosal lesions indicated serious morbidity</td>
</tr>
<tr>
<td>4</td>
<td>Reversal of lesions</td>
<td>None</td>
<td>Mucosal and cutaneous lesions resolved</td>
<td>Death from unrelated cause</td>
</tr>
<tr>
<td>5</td>
<td>Reversal of lesions</td>
<td>Drugs not discontinued and CS not started for 2 days after recommended</td>
<td>Recovery</td>
<td>Potential litigation</td>
</tr>
<tr>
<td>6</td>
<td>Reversal of lesions</td>
<td>None</td>
<td>Recovery</td>
<td>Traveling to multiple cities; initially seen in emergency rooms; treated with penicillin for presumptive infections; initial severe erythema and postural hypotension</td>
</tr>
<tr>
<td>7</td>
<td>Dramatic reversal of disease; patient had been moribund</td>
<td>None</td>
<td>Recovery except for renal disease</td>
<td>Total loss of skin and fingernails; had severe toxicity and pain and residual glomerulonephritis; litigation regarding penicillin allergy</td>
</tr>
<tr>
<td>8</td>
<td>Reversal of lesions</td>
<td>None</td>
<td>Recovery</td>
<td>Recovery but persistent liver function abnormalities related to viral hepatitis</td>
</tr>
<tr>
<td>9</td>
<td>Reversal of lesions</td>
<td>Consultant advised against use of CS</td>
<td>Recovery</td>
<td>AI faculty considered patient's problem sufficiently severe that death was expected</td>
</tr>
<tr>
<td>10</td>
<td>Reversal of lesions</td>
<td>None</td>
<td>Recovery</td>
<td>Decline in hemoglobin due to intravascular hemolysis</td>
</tr>
<tr>
<td>11</td>
<td>Reversal of lesions</td>
<td>None</td>
<td>Recovery</td>
<td>Decline in hemoglobin; proteinuria</td>
</tr>
<tr>
<td>12</td>
<td>Reversal of lesions</td>
<td>Consultant advised against use of CS</td>
<td>Recovery</td>
<td>Development of herpetic esophagitis (4 cultures) on day 6; treated successfully with IV acyclovir</td>
</tr>
<tr>
<td>13</td>
<td>Improvement of lesions</td>
<td>Consultant advised against use of CS</td>
<td>Recovery</td>
<td>Metastatic melanoma</td>
</tr>
</tbody>
</table>

*CS, Corticosteroids.
3. The severity of the final status of the disease cannot be predicted by the initial manifestations, nor can the rate of progression of the disease be predicted from initial manifestations.

4. Controversy may occur between managing and consulting physicians in regard to management. Potential litigation must be considered in regard to possible drug allergy or controversy about management.

5. The etiology in relation to drug allergy cannot be proven because the repeat administration of a suspected drug to prove that drug as the cause of Stevens-Johnson syndrome is unethical, in our opinion.

6. Severe Stevens-Johnson syndrome is sufficiently uncommon that few physicians see many cases.

**Suggested Management**

1. Immediately terminate suspected drugs and all nonessential drugs, and substitute alternate drugs for drugs suspected but considered essential.

2. Begin therapy with prednisone, at least 1 mg/kg/day or equivalent intravenous therapy.

3. Evaluate immediately for infection, and initiate therapy if indicated.

4. Consultations depending on degree and sites of involvement:
   A. Infectious disease
   B. Ophthalmology for ocular involvement
   C. Dermatology for management of bullous and exfoliative lesions
   D. Plastic surgery

5. Fluid replacement, pain control, and nutritional replacement as indicated by severity of disease.

6. Subsequent to recovery, if a drug suspected of causing the Stevens-Johnson syndrome is considered essential, the drug should only be readministered in very low slowly progressive doses over days by an expert in such test dose procedures, with adequate informed consent of the patient. Extreme caution is indicated.

**REFERENCES**


3. Ashley DW, Lazar T. Erythema multiforme exudativum major (Stevens-Johnson syndrome). Lancet 1951; 1:1091-95


10. Lookingbill DP. Drug eruptions. In: Hoekelman RA, Blatman

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This course, co-sponsored by New York Academy of Sciences and Royal Society of Medicine will be held October 1-3 at the Royal College of Surgeons, London, England. For information, contact the Conference Department, New York Academy of Sciences, 2 East 63rd Street, New York City 10021 (212:838-0230 (Fax: 212:888-2894).

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Erythema Multiforme and Stevens-Johnson Syndrome (Patterson et al)