Successful Treatment of Complex Aphthosis With Colchicine and Dapsone

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Objective: To investigate the effectiveness of colchicine and dapsone, 2 corticosteroid-sparing anti-inflammatory agents, in the treatment of patients with complex aphthosis (recurrent oral and genital aphthous ulcers or severe, almost constant, multiple oral aphthae in the absence of Behc¸et syndrome).

Design: Retrospective review of medical records.

Setting: Tertiary care medical clinic.

Patients: Fifty-five patients with complex aphthosis evaluated and treated at Mayo Clinic between January 1, 1998, and July 31, 2007. All the patients were treated according to a therapeutic ladder, starting with colchicine and adding dapsone to treatment of patients who did not have a substantial response (>75% improvement) to colchicine or who discontinued colchicine use because of adverse effects.

Main Outcome Measures: A substantial response to therapy with colchicine alone, dapsone alone, or colchicine and dapsone combined.

Results: Most patients (44 [80%]) had a substantial response to therapy and had no serious adverse effects.

Conclusions: Colchicine and dapsone are effective, safe therapies for the treatment of complex aphthosis. Colchicine and dapsone, 2 established drugs also used for gout and leprosy, respectively, and for other dermatologic disorders, should be considered efficacious in the treatment of complex aphthosis.


RECURRENT APHTHOUS STomatitis (RAS) is the most common inflammatory ulcerative condition of the oral mucosa in North American persons.1 It is characterized by intermittent episodes of painful oral aphthae of any morphologic origin. It can be simple or complex. Simple aphthosis, which constitutes most cases of RAS, involves a few to several bouts of aphthae per year, with distinct ulcer-free periods.2 Complex aphthosis refers to an almost constant presence of multiple (≥3) oral ulcers, or recurrent oral and genital aphthae, and exclusion of Behc¸et syndrome.2,4 In some patients, complex aphthosis may eventually progress to Behc¸et syndrome; these patients should be observed.5

Individual aphthae can be described as minor, major, and herpetiform.2,7 Minor aphthous ulcers (80% of aphthae) are small (<1 cm) and superficial, are located on the buccal and labial mucosa, heal within days, and do not cause scarring. Major aphthous ulcers (10% of aphthae) are larger than the minor ulcers (>1 cm), are deeper, are slow to heal (weeks to months), and often leave a scar. Herpetiform aphthae (10% of aphthae) are small (1-3 mm) and have a grouped appearance, often coalescing into a larger plaque and healing spontaneously in 1 to 4 weeks.

Although complex aphthosis constitutes a small subset of RAS cases, it often causes marked pain and disability. Treatment is challenging. The 2 main goals of therapy are supportive symptom management and, potentially, the start of systemic suppressive therapy to modify the intensity and frequency of attacks. Patients with bothersome RAS may seek medical advice and are often treated with topical corticosteroids to relieve symptoms. For many patients, these agents provide sufficient symptomatic therapy. However, for patients whose disease is more severe, response to treatment varies, and relapse is common. Several systemic drugs have been used to treat complex aphthosis, including systemic corticosteroids, thalidomide, pentoxifylline, colchicine, and dapsone. Systemic corticosteroids offer symptomatic relief and the healing of ulcers but do not affect the disease course or provide long-term remission of complex aphthosis. Furthermore, serious risks are associated with long-term systemic corticosteroid use. Therefore, it is preferable to suppress complex aphthosis with
We retrospectively reviewed the medical records of 55 patients with complex aphthosis in whom conservative treatment had failed. Patients were evaluated and treated by 2 physicians (A.J.B. and R.S.R.) between January 1, 1998, and July 31, 2007, in the Department of Dermatology, Mayo Clinic. Patients who denied research authorization were excluded from the analysis. This study was approved by the Mayo Clinic Institutional Review Board.

To be classified as having symptomatic complex aphthosis, patients had to have (1) severe attacks, manifested by the presence of many lesions (>3) simultaneously, deep and scarring lesions, posterior location of oral aphthae, and lesions that healed slowly (>2 weeks) and (2) frequent attacks, occurring greater than 50% of the time, more frequently than 10 times per year, and with brief remissions or continuous oral lesions.

Recurrent aphthous stomatitis was diagnosed clinically, and, where appropriate, biopsies were performed to rule out other conditions, such as lichen planus, pemphigus vulgaris, and mucous membrane pemphigoid. Also, where appropriate, oral ulcers were swabbed for viral culture to rule out herpes simplex virus, and patch testing was performed to rule out oral allergic contact stomatitis.

Patients were evaluated for an underlying cause of oral aphthae (eg, connective tissue disease, vasculitis, vitamin deficiency, medication-induced aphthae, and celiac disease), with testing for levels of antinuclear antibody and antineutrophil cytoplasmic antibody; levels of iron, ferritin, folate, thiamin (vitamin B1), riboflavin (vitamin B2), vitamin B6, vitamin B12, and zinc; and plasmic antibody; levels of iron, ferritin, folate, thiamin (vitamin B1), riboflavin (vitamin B2), vitamin B6, vitamin B12, and zinc; and plasmic antibody; levels of iron, ferritin, folate, thiamin (vitamin B1), riboflavin (vitamin B2), vitamin B6, vitamin B12, and zinc; and plasmic antibody; levels of iron, ferritin, folate, thiamin (vitamin B1), riboflavin (vitamin B2), vitamin B6, vitamin B12, and zinc; and plasmic antibody; levels of iron, ferritin, folate, thiamin (vitamin B1), riboflavin (vitamin B2), vitamin B6, vitamin B12, and zinc; and plasmic antibody; levels of iron, ferritin, folate, thiamin (vitamin B1), riboflavin (vitamin B2), vitamin B6, vitamin B12, and zinc; 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### Table 1. Characteristics and Clinical Features of 55 Patients With Complex Aphthosis

<table>
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<th>Characteristic</th>
<th>Patients (N=55)</th>
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<tr>
<td>Age at presentation, y</td>
<td>Mean (SD) 41 (16)</td>
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<tr>
<td>Median (range)</td>
<td>40 (9-73)</td>
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<tr>
<td>Female sex, No. (%)</td>
<td>38 (69)</td>
</tr>
<tr>
<td>Duration of disease before presentation to Mayo Clinic, y</td>
<td>Mean (SD) 18 (17)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>13 (0.25-65)</td>
</tr>
<tr>
<td>Presentation, No. (%)</td>
<td>Oral aphthae only 45 (82)</td>
</tr>
<tr>
<td>Oral and genital aphthae</td>
<td>10 (18)</td>
</tr>
<tr>
<td>Follow-up from initiation of therapy at Mayo Clinic, y</td>
<td>Mean (SD) 1.6 (1.7)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>1.0 (0.1-7.2)</td>
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### RESULTS

Fifty-five patients met the inclusion criteria. Of these patients, 38 (69%) were female. The mean age was 41 years, and the median duration of disease before presentation to Mayo Clinic was 13 years (Table 1). Patients had tried multiple therapies, including topical corticosteroids, topical immunomodulators, and short courses of oral corticosteroids; however, the treatments had failed. Forty-five patients (82%) had oral aphthae only and 10 (18%) had oral and genital aphthae.

Treatment of 52 of the 55 patients (95%) was started with colchicine (Table 2). Of these 52 patients, 2 (4%) began treatment with colchicine and dapsone simultaneously because of the severity of their disease, and both patients had treatment success. The other 50 patients received colchicine as monotherapy; 30 of these patients (60%) achieved therapeutic success and did not need further treatment. In this subset of patients who had treatment success, 29 (97%) had at least 75% improvement.
and 1 patient (3%) had complete clearing of symptoms. Of patients who initially received colchicine alone, 13 (26%) did not have a response to the medication and 7 (14%) had adverse effects. These 20 patients discontinued colchicine monotherapy. Among them, 6 did not receive a subsequent prescription for dapsone, 5 did not return for follow-up, and 1 had a previous anaphylactic reaction to a sulfa medication and, thus, was given pentoxifylline therapy, which was successful.

The next agent on the therapeutic ladder was dapsone (Table 2). Fourteen patients received combination therapy with colchicine and dapsone simultaneously; of these patients, 10 (71%) had treatment success, of whom 8 (80%) had at least 75% improvement and 2 (20%) had complete clearing of symptoms.

Five patients received dapsone as monotherapy—2 because they discontinued colchicine treatment owing to adverse effects and 3 because they had gastrointestinal tract intolerance to colchicine before we evaluated them. Of the patients taking dapsone as monotherapy, 4 (80%) had treatment success, with 3 of these 4 patients having at least 75% improvement.

Overall, 44 patients (80%) had treatment success with the therapeautic ladder. Patients noted the benefit within 4 to 8 weeks, with maximum benefit by 12 weeks. Median follow-up from the start of drug administration was 1.0 year (range, 0.1-7.2 years).

Twenty-one of 52 patients experienced adverse effects while taking colchicine, necessitating its discontinuation in 7 patients. The most common adverse effect was diarrhea (31%; 16 of 52), which caused 4 patients (8%) to discontinue colchicine therapy. Five other adverse effects of colchicine use occurred once each in the study: a burning sensation in the feet and transient thrombocytopenia, neither of which required therapy discontinuation, and rash with elevated liver enzyme levels, easy bruising, and vomiting, all 3 of which necessitated discontinuation.

Eleven of 19 patients had adverse effects while taking dapsone, necessitating its discontinuation in 3 patients. The most common adverse effect was hemolytic anemia (37%; 7 of 19). This effect necessitated discontinuation of therapy in 2 patients (11%) who were symptomatic. One patient had hyperbilirubinemia secondary to hemolytic anemia. Only 3 other adverse effects were reported by patients taking dapsone: transient leukopenia, paresthesia of the face, and asymptomatic dermatitis. Because dapsone therapy has been associated with peripheral neuropathic disease, it was discontinued in the patient with paresthesia, although a careful neurologic evaluation did not show peripheral neuropathy.

Colchicine has shown promise for the treatment of complex aphthosis.\(^9\)\(^\text{12}\) The postulated mechanism is interference with neutrophil function and migration.\(^12\) Although dapsone is frequently mentioned in the medical literature as a possible systemic therapy for complex aphthosis, few published studies describe its use for oral aphthae. Most studies\(^13\)\(^\text{15}\) involve small numbers of patients with Behçet syndrome. Dapsone is thought to be effective in complex aphthosis by impairing neutrophil function, chemotaxis, and migration.\(^16\)

This study demonstrates that colchicine is an effective first-line corticosteroid-sparing therapy for complex aphthosis, and these results offer promise for colchicine as a first-line systemic therapy. Of the 50 patients who received colchicine, 30 (60%) had treatment success with this agent alone. This response exceeds the success rate of the cohort described by Letsinger et al,\(^2\) of whom 28% (11 of 40) responded to colchicine as monotherapy.

The present study also demonstrates that dapsone is an effective second-line systemic treatment for complex aphthosis. Of patients taking dapsone alone, 80% (4 of 5) responded, and 71% (10 of 14) responded while taking colchicine and dapsone simultaneously. Overall, 74% (14 of 19) of the patients responded to dapsone.

Dapsone is an often-cited systemic treatment for RAS; however, few studies have evaluated its effectiveness in patients with complex aphthosis. Sharque et al\(^15\) found that dapsone was effective at decreasing the number, duration, and frequency of oral ulcers in 20 patients with Behçet syndrome. Letsinger et al\(^2\) found that dapsone alone was effective in only 7% of patients (2 of 27), but, when used with colchicine, dapsone was effective in 57% (12 of 21).

In the present study, there were no serious adverse events. Diarrhea was the most common adverse effect in patients taking colchicine. Gastrointestinal tract upset is usually dose related, and these patients frequently eliminated their gastrointestinal tract irritation by decreasing the dose. Only 4 patients (8%) discontinued colchicine treatment because of this adverse effect. Thus, in addition to being an efficacious treatment for complex aphthosis, colchicine therapy can be maintained long-term because it is safe and well tolerated with regular follow-up and monitoring.

The most common adverse effect of dapsone use in these patients was hemolytic anemia, which occurred in 37% (7 of 19) of patients. This effect was transient, however, and caused discontinuation of the drug in only 2 patients. The hemolytic anemia associated with dapsone therapy typically results in a decrease of 1 to 2 g/dL in hemoglobin level (to convert to grams per liter, multiply by 10) in the first 6 to 8 weeks of treatment, but this change is usually well tolerated by most patients.\(^17\) In fact, 2 patients did not have fatigue associated with their anemia. In the present patients with hemolytic anemia, it was discontinued in the

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<th>Therapy</th>
<th>Treatment Success, No./Total No. (%)</th>
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<tr>
<td>Colchicine alone</td>
<td>30/50 (60)</td>
</tr>
<tr>
<td>Colchicine and dapsone</td>
<td>10/14 (71)</td>
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<tr>
<td>Dapsone alone</td>
<td>4/5 (80)</td>
</tr>
<tr>
<td>Overall</td>
<td>44/55 (80)</td>
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\(^a\)Symptom improvement of 50% or greater.
emia, hemoglobin levels ranged from 8.5 to 11.0 g/dL. However, symptoms did not correlate with hemoglobin levels. For example, the patient with a hemoglobin level of 11.0 g/dL experienced the most severe symptoms. Reticulocytosis partially compensates for the anemia. A decrease in hemoglobin concentration is not an indication to discontinue dapsone treatment unless the decrease is more precipitous, with a resultant hemoglobin level of less than 10.0 g/dL or if the patient becomes symptomatic. Laboratory monitoring of hemoglobin level is important, especially early in therapy, because a decreasing level is an early adverse effect. Anemia occurred in the first 2 months in all but 1 patient. One patient had hyperbilirubinemia due to hemolytic anemia.

This series shows that colchicine and dapsone are effective and safe for the treatment of complex aphthosis. Similar to the treatment of other dermatologic conditions, additive and combination therapy often is more efficacious than monotherapy. In practice, we tend to follow the therapeutic ladder for additive therapies rather than abandoning one therapy in favor of another. Thus, we suggest that patients whose complex aphthosis does not respond to colchicine in their initial therapeutic trial continue taking colchicine when dapsone is added to the regimen.

This stepwise treatment of complex aphthosis adheres to the principle that the benefits conferred by a medication must be weighed against its risks. Colchicine is well tolerated, with adverse effects that are due mostly to gastrointestinal tract intolerance. A study of 350 children with familial Mediterranean fever treated with long-term (6-13 years) colchicine therapy (1-2 mg daily) highlights the safety of this drug. In the study, adverse effects of colchicine were unremarkable—mostly diarrhea and nausea—and did not prompt permanent discontinuation of treatment in any of the children. The next step, dapsone therapy, requires rigorous monitoring and has a potentially serious adverse effect profile. However, dapsone was well tolerated by the present patients. Furthermore, the long-term use of dapsone carries a relatively low risk of irreversible adverse effects. The safe use of dapsone is well established in its long history as a treatment for leprosy and dermatitis herpetiformis and as a prophylaxis against malaria.

We recognize that a retrospective review of patient medical records is not optimal; however, we benefited from the consistency of having only 2 physicians making the diagnosis, managing the treatment, and conducting follow-up assessments. Further limitations include the lack of standardized patient evaluation and the small number of patients treated with dapsone. In addition, Mayo Clinic, as a tertiary care center, may have a referral bias in favoring patients with more complex disease that did not respond to a variety of more conservative therapies, and we could not standardize these initial therapies. A further limitation was that many patients could not return to Mayo Clinic for follow-up because of the distance from the clinic and, thus, were excluded from this study.

In this retrospective review, therapy with colchicine, dapsone, or both resulted in excellent disease control in most patients (80%; 44 of 55) with complex aphthosis, a debilitating and problematic disease. These well-established drugs should be considered important “rungs” on the therapeutic ladder for complex aphthosis and efficacious in the treatment armamentarium for this disease. Furthermore, prospective, double-blind, randomized, placebo-controlled studies are needed to assess the optimal overall treatment of complex aphthosis.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lynde, Bruce, and Rogers. Acquisition of data: Rogers. Analysis and interpretation of data: Lynde, Bruce, and Rogers. Drafting of the manuscript: Lynde. Critical revision of the manuscript for important intellectual content: Lynde, Bruce, and Rogers. Study supervision: Bruce and Rogers.

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