Treatment of linear IgA bullous dermatosis of childhood with flucloxacillin

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Background: Linear IgA bullous dermatosis of childhood is a rare autoimmune bullous disease that mainly affects preschool-aged children. Dapsone is considered the first-line therapy with prompt response from most patients. However, it may be contraindicated in certain conditions such as glucose-6-phosphate dehydrogenase deficiency.

Objective: We sought to assess the efficacy of flucloxacillin in the treatment of linear IgA bullous dermatosis.

Methods: This is an observational study in which all confirmed cases of linear IgA bullous dermatosis (by both histological and immunofluorescence studies) will be treated with flucloxacillin. Flucloxacillin will be continued according to the response or otherwise will be discontinued after 8 weeks in the case of resistance.

Results: We describe 7 patients with linear IgA bullous dermatosis of childhood treated with flucloxacillin. In 4 cases, it induced complete remission within 3 to 4 months of starting therapy with no relapses. In the other 3 cases, it successfully controlled the disease but with prompt relapse on discontinuation of the treatment.

Limitations: This is a case series study with a small number of patients.

Conclusion: Flucloxacillin may be considered among the first alternative therapies for linear IgA bullous dermatosis of childhood. Further evaluation of the efficacy and safety of the long-term use is required.

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Linear IgA bullous dermatosis of childhood is a rare autoimmune vesicobullous disease. It mainly affects children at preschool age although newborns and adolescents have been affected.1-3 It is a self-limited disease with an average duration of 2 years.4-6 Dapsone is the standard treatment with excellent control in most cases.5-9 However, resistant cases have been reported. Other treatment modalities that have been effective include systemic corticosteroids and colchicine.1,10-12 Oxacillin and dicloxacillin have recently been reported as effective therapies for linear IgA bullous dermatosis of childhood.13-15 Other immunobullous diseases including bullous pemphigoid and linear IgA bullous dermatosis of adulthood have responded to different antibiotics including tetracyclines and erythromycin.16-23 Herein we describe 7 cases of linear IgA bullous dermatosis of childhood treated effectively with flucloxacillin, causing rapid and lasting remission in 4 cases and excellent control in the remaining ones.

CASE SUMMARIES

Case 1

A 5-year-old boy had pruritic tense blisters for 3.5 years. Blisters primarily affected his flexures, perioral, and buccal mucosae. Histologic study of the skin biopsy specimen showed a subepidermal blister with neutrophilic and scant eosinophilic infiltrates. Strong positive linear deposition of IgA autoantibodies at the dermoepidermal junction was evident.
with direct immunofluorescence study. A very low serum level of glucose-6-phosphate dehydrogenase (G6PD) was detected at baseline investigations, which precluded usage of dapsone. Flucloxacillin (250 mg every 8 hours) was initiated and subsequently increased to 500 mg every 8 hours before it showed marked improvement. The treatment continued for 6 months with complete clearance. When flucloxacillin was stopped, blisters appeared within a week. Colchicine (1.5 mg in 3 divided doses) was tried with poor response in spite of a 4-month course. Flucloxacillin was then resumed at a dose of 500 mg every 8 hours, which brought prompt and complete control of blisters. Flucloxacillin was continued for 6 years. Whenever it was withheld, relapse was experienced (Fig 1). Periodic laboratory screening for complete blood cell counts and liver function was consistently within normal values. The patient did not have any noticeable side effects from the treatment.

**Cases summaries**

Brief details about all cases are summarized in Table I. Cases were divided into groups I and II according to the time onset of flucloxacillin therapy in the course of the disease (early vs late).

**DISCUSSION**

Linear IgA bullous dermatosis of childhood responds well to dapsone. However, resistant cases are well documented in the literature. Moreover, dapsone may be contraindicated in conditions such as G6PD deficiency, hypersensitivity syndrome to dapsone, severe hemolytic anemia, and bone marrow suppression. As such, several drugs have been reported in the treatment of linear IgA bullous dermatosis of childhood with variable response including colchicine, trimethoprim, sulfapyridine, oxacillin, and dicloxacillin. It is not unusual for antibiotics to be used in immunobullous diseases. Tetracyclines have been established as a good alternative for treatment of bullous pemphigoid.

In the first patient of this series, we gave flucloxacillin instead of dapsone after discovering the low serum levels of G6PD. After this successful trial, we extended our experience in the following cases in spite of normal G6PD levels. Collectively, 7 patients with linear IgA bullous dermatosis of childhood have been treated with flucloxacillin. Based on their response to treatments, we sought to divide them into two groups. The first group included cases in which flucloxacillin was started after more than 1 year of disease onset, whereas in the second group it was started within 1 month of the disease onset.

In the first group (Table I), systemic corticosteroids with or without dapsone were used, which brought a good response but with instant relapse on withholding the treatment. After starting flucloxacillin, prompt response was observed in all patients of this group. However, relapses were also prompt on discontinuation of treatment. The quick responses and relapses with starting or withholding flucloxacillin are in favor of its effectiveness rather than the spontaneous remission. In the second group (Table I), there was no prior therapy to flucloxacillin and it was started very early in the course of the disease. Interestingly, all patients had complete remissions within 3 to 4 months without any relapses after stopping the treatment. It may be difficult to conclude whether such remissions are related to flucloxacillin or spontaneous. However, it is very unusual for linear IgA bullous dermatosis of childhood to remit before 2 years. In this group, we speculate that the initiation of treatment early on in the course of the disease (within 1 month) may be the decisive factor in inducing early remission.

Oxacillin and dicloxacillin have been successfully used for linear IgA bullous dermatosis of childhood. A summary of the reported case series are shown in Table II. Based on these observations, it is not adequately clear that the early onset of therapy made the differences in remission. The mechanism by which these antibiotics work in immunobullous diseases is not known. However, the anti-inflammatory properties of these antibiotics are the likely mechanism of action. Aho and Mannisto were able to show in vitro the ability of doxycycline in preventing migration of polymorphonuclear leukocyte that was not the case for erythromycin. In another experiment by Selenke et al, the erythromycin group showed steroid-sparing effects in patients with bronchial asthma that was possibly attributed to the anti-inflammatory properties. The other possible mechanism for these antibiotics in cases of linear IgA bullous dermatosis of childhood is an immune
### Table I. Case summaries for linear IgA bullous dermatosis of childhood treated with flucloxacillin

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (sex)</th>
<th>Duration of disease</th>
<th>Previous condition</th>
<th>Dx</th>
<th>Previous treatment</th>
<th>Duration on flucloxacillin</th>
<th>Dosage of flucloxacillin</th>
<th>Response</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.25 y (Male)</td>
<td>3.5 y</td>
<td>G6PD deficiency</td>
<td>Bx and DIF</td>
<td>PO steroid + others</td>
<td>6 y</td>
<td>500 mg QID then 500 mg TID</td>
<td>Complete clearing</td>
<td>Relapse on flucloxacillin D/C</td>
</tr>
<tr>
<td>2</td>
<td>3.75 y (Female)</td>
<td>11 mo</td>
<td>None</td>
<td>Bx and DIF</td>
<td>Dapsone and PO steroid</td>
<td>4 y</td>
<td>500 mg QID then 250 mg TID</td>
<td>Complete clearing</td>
<td>Relapse on flucloxacillin D/C</td>
</tr>
<tr>
<td>3</td>
<td>4 y (Male)</td>
<td>1.25 y</td>
<td>Hypochromic microcytiaemia</td>
<td>Bx and DIF</td>
<td>PO steroid</td>
<td>3 y</td>
<td>180 mg TID</td>
<td>Complete clearing</td>
<td>Relapse on flucloxacillin D/C and remission after 3 y</td>
</tr>
</tbody>
</table>

**Group II:** Early treatment with flucloxacillin

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (sex)</th>
<th>Duration of disease</th>
<th>Previous condition</th>
<th>Dx</th>
<th>Previous treatment</th>
<th>Duration on flucloxacillin</th>
<th>Dosage of flucloxacillin</th>
<th>Response</th>
<th>Remarks and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>7.5 y (Male)</td>
<td>2 wk</td>
<td>Juvenile intestinal polyposis</td>
<td>Bx and DIF</td>
<td>None</td>
<td>3 mo</td>
<td>500 mg QID then 250 mg BID</td>
<td>Remission</td>
<td>5 y no relapse</td>
</tr>
<tr>
<td>5</td>
<td>1.25 y (Female)</td>
<td>4 wk</td>
<td>URTI</td>
<td>Bx and DIF</td>
<td>None</td>
<td>3 mo</td>
<td>150 mg QID then 150 mg BID</td>
<td>Remission</td>
<td>4 y no relapse</td>
</tr>
<tr>
<td>6</td>
<td>1.5 y (Female)</td>
<td>4 wk</td>
<td>URTI</td>
<td>Bx and DIF</td>
<td>None</td>
<td>4 mo</td>
<td>200 mg QID then 200 mg TID</td>
<td>Remission</td>
<td>4 y no relapse</td>
</tr>
<tr>
<td>7</td>
<td>6 y (Male)</td>
<td>10 d</td>
<td>None</td>
<td>Bx and DIF</td>
<td>None</td>
<td>2.5 mo</td>
<td>250 mg QID then 250 mg BID</td>
<td>Remission</td>
<td>2 y no relapse</td>
</tr>
</tbody>
</table>

BID, Twice a day; Bx, biopsy; DIF, direct immunofluorescence; Dx, diagnosis; D/C, discontinuation; G6PD, glucose-6-phosphate dehydrogenase; PO, per oral; QID, 4 times a day; TID, 3 times a day; URTI, upper respiratory tract infection.

### Table II. Summary of the published cases of linear IgA bullous dermatosis of childhood treated with similar antibiotics

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age (sex)</th>
<th>Duration of disease</th>
<th>Previous treatment</th>
<th>Duration on (antibiotic)</th>
<th>Response</th>
<th>Remarks and follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denguezi et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A (Oxacillin)</td>
<td>Remission</td>
<td>N/A</td>
</tr>
<tr>
<td>Denguezi et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A (Oxacillin)</td>
<td>Remission</td>
<td>N/A</td>
</tr>
<tr>
<td>Denguezi et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A (Oxacillin)</td>
<td>Remission</td>
<td>N/A</td>
</tr>
<tr>
<td>Skinner et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>6 y (Male)</td>
<td>Acute eruption</td>
<td>None</td>
<td>3.5 y (Dicloxacillin)</td>
<td>Complete clearing</td>
<td>Relapse on dicloxacillin D/C and remission after 3.5 y</td>
</tr>
<tr>
<td>Skinner et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>2.5 y (Male)</td>
<td>Several wk</td>
<td>Cefaclor</td>
<td>N/A (Dicloxacillin)</td>
<td>Complete clearing</td>
<td>Relapse on dicloxacillin D/C</td>
</tr>
<tr>
<td>Skinner et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>5 y (Male)</td>
<td>2 y</td>
<td>Prednisolone and dapsone</td>
<td>N/A (Dicloxacillin)</td>
<td>Complete clearing</td>
<td>Relapse on dicloxacillin D/C</td>
</tr>
<tr>
<td>Siegfried and Sirawan&lt;sup&gt;15&lt;/sup&gt;</td>
<td>5.5 y (Female)</td>
<td>3 mo</td>
<td>Prednisolone, dapsone, acyclovir, and cefprozil</td>
<td>1 y (Dicloxacillin)</td>
<td>Complete clearing</td>
<td>Remission after 1 y</td>
</tr>
<tr>
<td>Siegfried and Sirawan&lt;sup&gt;15&lt;/sup&gt;</td>
<td>9 y (Female)</td>
<td>6 mo</td>
<td>Prednisolone</td>
<td>2 y (Dicloxacillin)</td>
<td>Complete clearing</td>
<td>Relapse on dicloxacillin D/C</td>
</tr>
</tbody>
</table>

D/C, Discontinuation; N/A, not available.
reaction to flucloxacillin-/dicloxacillin-sensitive bacteria, perhaps *Staphylococcus aureus*, which is aborted or curtailed once these antibiotics are started.

The confusion between linear IgA bullous dermatosis of childhood and bullous impetigo is clinically possible, yet all our cases had direct immunofluorescence confirmation. The hypothesis of an infective organism triggering an immunologic reaction responsible for linear IgA bullous dermatosis of childhood has been discussed in the literature. Different infections such as *Salmonella enteritis*, nonspecific gastrointestinal infection, and Epstein-Barr virus infection have been associated with linear IgA bullous dermatosis of childhood.\(^{29-30}\) Interestingly, in the report of *Salmonella* enteritis, the patient had been started on flucloxacillin before developing linear IgA bullous dermatosis of childhood. It is not clear whether the development of this immunobullous eruption is related to the infection, the treatment, both, or neither. The authors of this article were in favor of infection as the possible cause. Two of our patients (cases 5 and 6) had an upper respiratory tract infection preceding the disease, and in the third one (case 7), *Streptococcus* group A was isolated from one of the blisters. Overall, the causative relationship between linear IgA bullous dermatosis of childhood and infection is not yet adequately supported.

Flucloxacillin is relatively safe for short courses as is evident by its wide use in bacterial infections both in children and adults.\(^{31}\) However, a major adverse effect of flucloxacillin is a cholestatic hepatitis that might rarely be fatal.\(^{32-34}\) Other very rare but significant adverse effects of flucloxacillin include aplastic anemia, hemolytic anemia, agranulocytosis, and acute interstitial nephritis.\(^{35-38}\) In conclusion, flucloxacillin may be included among the first alternative therapies for linear IgA bullous dermatosis of childhood and when administered early on the course of the disease, it may induce quick and long-lasting remission. Liver enzyme monitoring is recommended. Further evaluation of both the efficacy and safety of flucloxacillin in linear IgA bullous dermatosis of childhood is required.

**REFERENCES**


29. Wilk M, Biwer E. Chronic bullous dermatosis in childhood (linear IgA dermatosis) [in German]. Hautarzt 1993;44:470-5.


