Short title running head: Bronchiolitis obliterans as long-term sequela of SJS/TEN in children

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Bronchiolitis obliterans as a long-term sequela of Stevens–Johnson syndrome and toxic epidermal necrolysis in children

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# Summary

Toxic epidermal necrolysis (TEN) and Stevens–Johnson syndrome (SJS) are characterized by widespread skin and mucosal blistering and necrosis. The triggers and long-term sequelae in children may differ from those reported for adults. Bronchiolitis obliterans (BO) is an uncommon complication, with only 15 previously reported cases, but can lead to significant long-term morbidity, requiring lung transplantation in some cases. We report three children with nondrug-related SJS (*n* = 1) TEN (*n* = 2) who developed BO. Two were treated with intravenous immunoglobulin therapy (2–2.4 g/kg) and all three survived. We highlight salient learning points from our cases and potential pitfalls in diagnosis of BO, including delayed onset, and we also review the literature.

Stevens–Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare, potentially life-threatening conditions; characterized by widespread skin and mucosal necrosis. SJS is defined as < 10% body surface area (BSA) detachment, SJS–TEN overlap as 10–30% BSA detachment and TEN as > 30% detachment.1 The reported incidence is lower in children than adults: 5.3 vs. 9.3, 0.8 vs. 1.9 and 0.4 vs. 1.6 cases per million per year for SJS, SJS–TEN and TEN, respectively, in the USA.2,3 Medications are usually culpable, although infections may be implicated, particularly in children.4 Mortality in childhood is reportedly 0% (SJS), 4% (SJS-TEN) and 16% (TEN),2 with deaths most frequently due to sepsis and organ failure.2 However, similarly to adults, increased mortality is noted with higher degrees of epidermal detachment: 60–70% body surface area (BSA) involvement was associated with 37.5% mortality in one study.4 Intravenous immunoglobulin (IVIG), ciclosporin and/or systemic corticosteroids have been used despite the relative lack of evidence, as summarized in recent guidelines.6 Bronchiolitis obliterans (BO) is a rarely reported complication, but when present, is associated with significant long-term morbidity. We report three children with nondrug-related SJS/TEN who developed BO.

# Report

Patient 1 was a previously well 5-year-old boy who presented with a 2-day history of an erythematous maculopapular rash in association with fever and coryza. Overall, the skin changes involved 95% BSA, with 40% epidermal detachment. There were additional bilateral conjunctival defects with confluent superficial punctate epithelial erosions of the cornea. He had severe oral and upper airway ulceration with sloughing. Subsequent development of stridor necessitated intubation.

Histological examination of a skin biopsy confirmed TEN, with negative direct immunofluorescence. Chest radiography was unremarkable. Bronchoscopy showed ulceration at the base of insertion of the endotracheal tube. *Pseudomonas aeruginosa* was cultured from bronchoalveolar lavage (BAL) and adenovirus, rhinovirus and enterovirus from nasopharyngeal aspirate (NPA). *Mycoplasma* IgG titre was 1 : 320 (weakly positive). The patient received IVIg 2 g/kg over 2 days. Skin re-epithelialization occurred within 3 weeks. Conjunctival inflammation progressed with increasing cicatrisation. The patient required four sets of amniotic membrane transplant (AMT) for the corneal epithelial defects and multiple skin debridements under anaesthesia. He subsequently received pulsed IV methylprednisolone and mycophenolate mofetil (MMF) (20 mg/kg/day for 3 days), then oral prednisolone (2.25 mg/kg/day prednisolone for 1 month, which was gradually weaned over 3 months), alongside MMF 600 mg/m2/day and ciclosporin eye drops to reduce ocular inflammation. He is currently awaiting a corneal stem cell transplant.

Five months later, he developed exertional dyspnoea and a nonproductive cough. Spirometry showed a showed a significant nonreversible obstructive picture [reduced forced expiratory volume in 1 second (FEV1) was 29% predicted, forced vital capacity (FVC) was 55% predicted, and no reversibility was seen with inhaled salbutamol]. Chest X-ray showed mild bronchial wall thickening in the right middle lobe. High-resolution computed tomography of the chest (HRCT) showed mosaic perfusion and air trapping on expiratory films, characteristic of BO (Fig. 1). Treatment with fluticasone proprionate, oscillating positive expiratory pressure (PEP) physiotherapy, azithromycin prophylaxis (200 mg daily, 3 times/week) and rescue courses of oral amoxicillin/clavulanic acid for infective exacerbations ameliorated pulmonary function. After 1 year, FEV1 was 71% predicted.

Patient 2 was a previously well 5-year-old boy who had a sore throat and fever for 11 days before developing a diffuse erythematous rash, which became bullous over 24 h. There was 26% skin detachment noted, with prominent oral ulceration and conjunctival injection. TEN was subsequently confirmed histologically on skin biopsy, with negative direct immunofluorescence. IVIg was commenced (total 2.4 g/kg over 3 days). NPA detected adenovirus.

The skin re-epithelialized by day 26. Two weeks after discharge, the patient developed exertional dyspnoea. HRCT showed bilateral air trapping and vascular paucity, suggestive of BO. FEV1 and FVC were 48% and 66% predicted, respectively, without reversibility. Oral prednisolone 2 mg/kg daily for 2 weeks did not improve the symptoms. Management continued with anti-inflammatory strategies, including azithromycin 200 mg 3 times/week as prophylaxis and inhaled corticosteroids, alongside regular PEP physiotherapy.

Patient 3 was a previously well 14-year-old girl, who developed cutaneous blistering, severe oral mucosal ulceration and eye pain 1 week after developing a sore throat and cough. She had multiple targetoid lesions, including at acral sites, with 5% epidermal detachment with overlapping features of SJS and erythema multiforme. Chest radiography during admission was unremarkable. The patient was treated with intravenous ceftriaxone, aciclovir and oral azithromycin. Her skin and mouth rapidly improved within 7 days. Blepharitis was treated with dexamethasone eye drops and chloramphenicol ointment four times daily. *Mycoplasma* *pneumoniae* serology was subsequently positive (complement fixation test titre > 64, agglutination test > 1280).

At review 4 weeks later, the patient reported breathlessness on exertion and wheeze. Spirometry showed a significant nonreversible obstructive picture (FEV1 was 25% predicted without reversibility) and HRCT confirmed BO. In view of the severe symptoms, further treatment included IV methylprednisolone 10 mg/kg for 3 consecutive days per month for 6 months in addition to azithromycin, inhaled ciclesonide and PEP physiotherapy. At 6 months after starting treatment, there was minimal improvement in FEV1, which was 33% predicted. She also remains under Ophthalmology follow-up with persistent meibomian gland dysfunction, subtarsal scarring and papillary conjunctivitis, requiring long-term sodium hyaluronate eye lubrication.

BO is an uncommon fibrosing chronic lung disease, which occurs following a severe lower respiratory tract insult leading to narrowing and/or obliteration of the small airways7. It is characterized clinically by tachypnoea, crackles, wheezing, increased anteroposterior chest diameter and hypoxaemia.8 Pulmonary function tests typically show varying degrees of obstruction with a limited response to bronchodilators. Chest radiography is nonspecific but possible changes include hyperexpansion, gas trapping and peribronchial thickening. HRCT is generally diagnostic, demonstrating mosaic perfusion, vascular attenuation and central bronchiectasis.8

The pathogenesis of BO is not fully understood but may include bronchial injury from primary blistering lesions, secondary lung infection or a type III immune mechanism. 8

BO is a well-defined complication of heart/lung, lung and bone marrow transplant. The commonest cause for BO in immunocompetent children is severe lower respiratory tract infection (LRTI), of which adenovirus is the most commonly documented cause worldwide9. It is only rarely reported after SJS or TEN. *M. pneumoniae* has also been associated with the development of BO.7 Evidence of both adenovirus and *Mycoplasma* were identified in two of our patients, and not tested in the third. The presence of adenovirus in the setting of SJS/TEN may hypothetically increase the risk of BO, therefore testing at diagnosis could be useful, but a formal study examining this potential link is needed.

BO is a rare disease and thus randomized controlled trials of treatments have not been performed, even for the more common postinfectious group. Empirical treatment recommendations from a review of postinfectious BO in children included inhaled corticosteroids, bronchodilators, rescue antibiotics to treat acute infection, and azithromycin for its anti-inflammatory and immunomodulatory properties.10 All three of our patients received azithromycin and demonstrated stable or improved lung function.

The use of systemic corticosteroids in the management of BO is contentious. One case report of postinfectious BO demonstrated improved lung function with pulsed corticosteroids, but most of the benefit was lost by 4 months, suggesting that long-term immunosuppression may be needed.11 No clear benefit was identified in our patients receiving systemic therapy early in the course of their disease; Patient 1 (IVIG initiated by dermatologists, and systemic corticosteroids and MMF initiated by ophthalmologists) and Patient 2 (IVIG initiated by dermatologists). Of note, Patient 3 did not receive systemic immunosuppressive or immunomodulatory therapy in the acute phase but developed the most severe symptoms of BO. It is unclear whether early intervention would have affected the development of BO and firm conclusions cannot be drawn from such small patient numbers.

Our literature review (MEDLINE database) identified only 15 described cases of BO in SJS and TEN in children (summarized in Table 1). In the published cases of BO following SJS/TEN, only 6 of 15 had a drug implicated. We speculate that infection may have been a trigger for SJS and TEN in the remainder; adenovirus was negative in one case but not mentioned in the rest. The characteristics of our cases were comparable to those in other reports: age of onset ranged from 5 to 14 years, and mean time to onset of respiratory symptoms following initial presentation with SJS/TEN ranged from 5 days to 5 months. There were no reports of pre-existing lung disease. One of our patients (Patient 1) had a very late onset of respiratory symptoms 5 months following the initial presentation with TEN. In general, based on the review of the published cases, the onset appears to be variable. This highlights that BO may develop insidiously, long after the initial mucocutaneous lesions have healed, emphasizing the need for close follow-up. Parents of affected children should be advised to be vigilant for symptoms of breathlessness.

Post-SJS and TEN, BO may be progressive; five of the published cases required lung transplantation, with one death reported in a transplant recipient and one death in another case. However, it is difficult to be certain that the literature captures late mortality that might be associated with BO. In a case series by Moonnumakal *et al*.,8 five patients with BO required lung transplantation; two were post-SJS, and none was post-LRTI. This may suggest a more aggressive disease course in SJS/TEN-related BO.

Early and aggressive treatment of acute ocular manifestations is essential to limit long-term sequelae and vision impairment in these patients, with evidence supporting the use of AMT. Ocular manifestations may also present late, necessitating follow-up in all patients.12

BO is an uncommon but important sequela of SJS and TEN, and Dermatologists should be aware of this. Onset can be insidious and may be several months after the initial episode. There is some evidence to suggest that BO may be more aggressive following SJS and TEN. Based on the experience from our cases, we would recommend checking adenovirus serology in all children presenting with SJS or TEN until further information on the association with post-SJS/TEN BO and adenovirus is available. Additionally, baseline pulmonary function tests following hospital discharge could be helpful to monitor for any early respiratory deterioration. Families should also be aware to seek review expediently if there are any new respiratory symptoms.

# Learning points

* SJS and TEN are triggered by infection more frequently in children than adults.
* BO is a severe fibrosing lung disease, which rarely develops after SJS/TEN.
* The onset may be insidious, sometimes many months after the acute episode of SJS/TEN, demonstrating the need for close follow-up.
* The initial chest X-ray may be falsely reassuring in BO; spirometry (to demonstrate an obstructive picture with lack of reversibility with bronchodilators) and HRCT are required for diagnosis.
* There is a lack of clear evidence to guide management, including systemic therapy, in BO.
* Post-SJS and TEN, BO may be progressive, and severe cases may require lung transplantation.
* Eye involvement is a significant cause of morbidity in children with SJS/TEN, with some patients having long-term sequelae including corneal damage, meibomian gland dysfunction and scarring.
* Dermatologists should consider checking adenovirus serology in all children with SJS/TEN, and pulmonary function tests in all children admitted with SJS/TEN following discharge.

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**Figure 1** (a,b) High-resolution computed tomography confirmed bronchiolitis obliterans with mosaic profusion and air trapping on (b) the expiratory scan.

**Figure 2** Patient 3: mucocutaneous changes showing overlapping morphological features of Stevens–Johnson syndrome and erythema multiforme on (a) face, (b) palm, (c) sole and (d) upper back. (e) Close-up showing ‘atypical’ target lesions/blisters. (f) Subsequent nail shedding at the 4-month follow-up.

**Table 1** Summary of cases of bronchiolitis obliterans post-Stevens–Johnson syndrome/toxic epidermal necrolysis from the literature and our own series.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Reference | Age, years | Culprit | BO onset after mucocutaneous features | Outcome |
| Kim *et* *al*., 199622 | 10 | Anti-TB treatment | 2 months | No progression |
| 6 | NS | 5 days | Some improvement |
| Date *et* *al*., 200220 | 13 | NS | 1 week | Successful lung transplant |
| Bakirtas *et* *al*., 200719 | 8 | NS | 2 weeks | Some improvement |
| 13 | NS | 5 months | Some improvement |
| Chiu *et* *al*., 200818 | 6 | NS | NS | Improved |
| 6 | NS | NS | Lung transplant, then died |
| Moonumakal *et* *al*., 20088 | NS | NS | NS | Required lung transplantation |
| NS | NS | NS | Required lung transplantation |
| Shoji *et* *al*., 201017 | 6 | Antibiotic (NS) | 2 weeks | Ventilator for 7 months, then lung transplant |
| Dogra *et* *al*., 201116 | 5 | Nimesulide | 2 weeks | Died after 1 year |
| Dogra *et* *al*., 201421 | 9 | Ibuprofen | 1 week | Improved |
| Wang *et* *al*., 201515 | 9 | Lamotrigine | 1 week | No progression |
| Sato *et* *al*., 201813 | 11 | Clarithromycin | NS | NS |
| Milheiro Silva *et* *al*., 201814 | 8 | NS | 4 weeks | Night oxygen required |
| Current report |  |  |  |  |
|  Patient 1 | 5 | Infection (ND) | 5 months | Some improvement |
|  Patient 2 | 5 | Adenovirus | 6 weeks | Some improvement |
|  Patient 3 | 15 | *Mycoplasma* | 4 weeks | Minimal improvement |

BO, bronchiolitis obliterans; ND, not determined, NS, not specified; TB, tuberculosis.