

# Diagnostic Challenges in a Pediatric Case of Recurrent Blistering Skin Reactions: Ibuprofen-Induced Fixed Drug Exanthema versus Infection-Triggered Erythema Multiforme

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**Abstract:** A 12-year-old patient was hospitalized with suspected recurrent Stevens-Johnson syndrome (SJS) caused by ibuprofen. The patient presented with aphthous lesions on the lips and oral mucosa, accompanied by fever and cough. Further examination revealed more severe symptoms. The exact classification of his skin reaction and the underlying cause were challenging due to the coexistence of multiple potential triggers. The diagnostic overlap among various skin reactions requires careful evaluation of the clinical presentation and histopathological findings in relation to potential drug exposure and/or infectious triggers. Cutaneous reactions such as SJS and fixed drug exanthema are predominantly associated with drug exposure, whereas Erythema multiforme (EM) and *Mycoplasma pneumoniae* rash and mucositis (MIRM) are mainly linked to infectious triggers. The diagnosis of a skin reaction and its trigger is highly relevant for therapy and prevention of further episodes. In this patient, administration of ibuprofen, as well as infections with Herpes simplex virus (HSV) and *Mycoplasma pneumoniae* (*M. pneumoniae*) were considered potential triggers, highlighting the complexity of this case. The patient recovered following extensive therapy and was discharged after two weeks.

**Keywords:** drug therapy safety, adverse drug reaction in children, pediatric case report, pediatric dermatology, NSAID reaction, skin reactions

## Introduction

A 12-year-old boy (35 kg, 148 cm) was admitted to the pediatric hospital. He had experienced fever, fatigue and cough for several days. Due to these symptoms, the patient received 5 mL of ibuprofen (40 mg/mL) twice at home over two days. After two days, he developed aphthous lesions on the lips and oral mucosa. In the clinical examination, swelling of the lips, blisters in the mouth, conjunctival redness in both eyes, marked fatigue, fever and cough were observed.

## Medical History

Since 2018, the patient has had four episodes of aphthous lesions accompanied by fever and fatigue. The first episode was in August 2018. Following a febrile infection treated with ibuprofen, aphthous lesions on the lips and oral mucosa were observed. The patient was hospitalized and during the following days, he developed blisters at the genitals and buttocks. The laboratory tests for HSV and *M. pneumoniae* were negative.

In February 2022, the patient presented to a physician again with aphthous lesions on the lips after administration of ibuprofen. Mucosal involvement was less pronounced in this episode. In the subsequent course, aphthous lesions

developed in the genital area. Skin reactions and involvement of the conjunctiva were not observed. He was not hospitalized during this episode.

After this episode, a prick test and Lymphocyte transformation test on ibuprofen were performed showing negative results. A patch test with in situ application at a previous reaction site with ibuprofen was never performed, although it had been recommended by previous physicians.<sup>1</sup> Nevertheless, the recurrence of skin lesions at the same site as in previous episodes strengthens the potential association with ibuprofen despite negative prick tests.<sup>2</sup>

Further episodes without hospitalization were recorded for October 2022 and April 2023. The intensity of the symptoms varied considerably in each episode. The precise doses of ibuprofen during previous episodes were not documented.

Nevertheless, for most of the described episodes a temporal relationship to the use of ibuprofen had been reported. Therefore, a recurrent SJS triggered by ibuprofen was suspected.

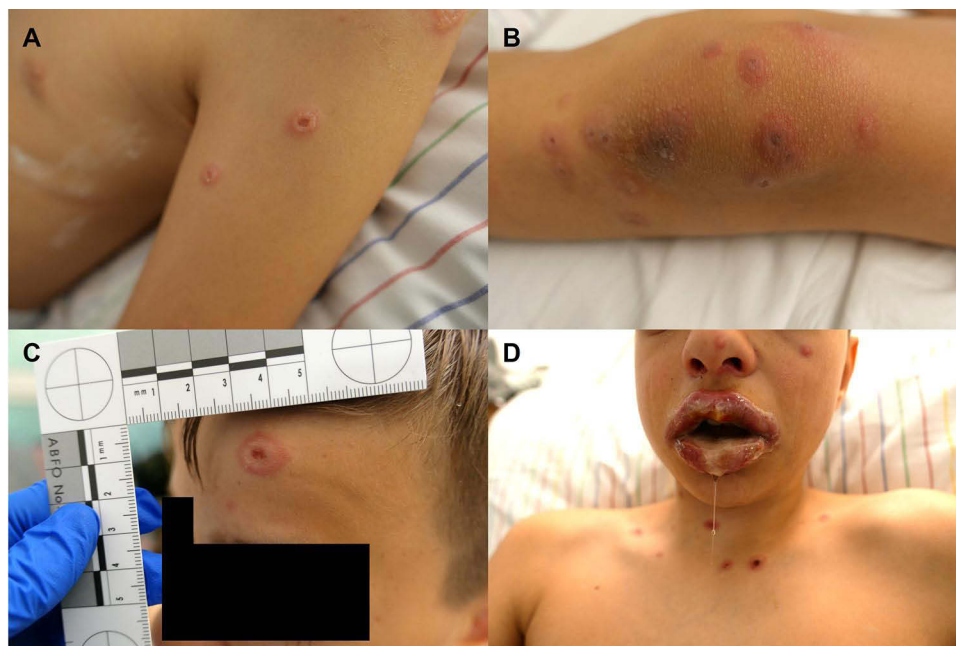
The patient had no other known previous illness and took no long-term medications. He was vaccinated according to the national guidelines.

## Clinical Progression

In the further clinical course of the reported episode, the patient showed a severe mucositis with a significant swelling of the lips and saliva formation (Figure 1). Moreover, he presented with a papular exanthema and blister formation, initially at the hands, upper arms and legs, extending to the trunk, genital area and face. The conjunctival redness in both eyes was associated with an acute hemorrhagic conjunctivitis, while uveitis was excluded by an ophthalmologist's consultation. Chest X-ray suggested mild infiltrates in the left mid-lung field on lateral view, consistent with pneumonia. No signs of pneumothorax or pleural effusion were detected during clinical examination.

Laboratory tests revealed increased values for leucocytes from day 1 to day 7 with a maximum on day 4. Additionally, thrombocyte levels were elevated on day 7. Moreover, C-reactive protein was increased from day 1 to day 4 before decreasing by day 7. Similarly, the blood sedimentation rate declined from day 1 to day 4 (Table 1).

Bacteriological and viral PCR and ELISA tests determined the presence of *M. pneumoniae* and HSV. The test for HSV was negative on day 3 after admission but positive on day 7. *M. pneumoniae* was positive on day 3 (Table 2).



**Figure 1** Blistering skin reaction and pronounced mucosal lesions in a 12-year-old patient. Skin blisters on the upper arm (A) and left knee (B) showing a typical cockade shape. (C) Extension of the skin blisters to the head area showing a diameter of approximately one centimetre. (D) Severe mucositis with significant swelling of lips accompanied by extensive saliva formation.

**Table 1** Important Laboratory Parameters on the Day of Admission to Hospital (Day 1), Day 4 and Day 7

<b>Blood</b>			
<b>Parameter (Reference)</b>	<b>Day 1</b>	<b>Day 4</b>	<b>Day 7</b>
Leucocytes (3.82–9.67) × 10 <sup>3</sup> /μL	16.63 × 10 <sup>3</sup> /μL ↑	16.85 × 10 <sup>3</sup> /μL ↑	12.84 × 10 <sup>3</sup> /μL ↑
Thrombocytes (159–368) × 10 <sup>3</sup> /μL	278 × 10 <sup>3</sup> /μL	317 × 10 <sup>3</sup> /μL	550 × 10 <sup>3</sup> /μL ↑
C-reactive protein (<5) mg/L	41.6 mg/L ↑	128.2 mg/L ↑	18.0 mg/L ↑
Blood sedimentation rate (<13) mm/h	41 mm/h ↑	32 mm/h ↑	N/A

**Abbreviations:** ↑, increased, N/A, not available.

**Table 2** Result of the Pathogen Detection on the Day of Admission to Hospital (Day 1), Day 3 and Day 7

<b>Microbiology</b>			
<b>Parameter</b>	<b>Day 1</b>	<b>Day 3</b>	<b>Day 7</b>
HSV (ELISA)	N/A	negative	positive
M. pneumoniae (PCR)	N/A	positive	N/A

**Abbreviation:** N/A, not available.

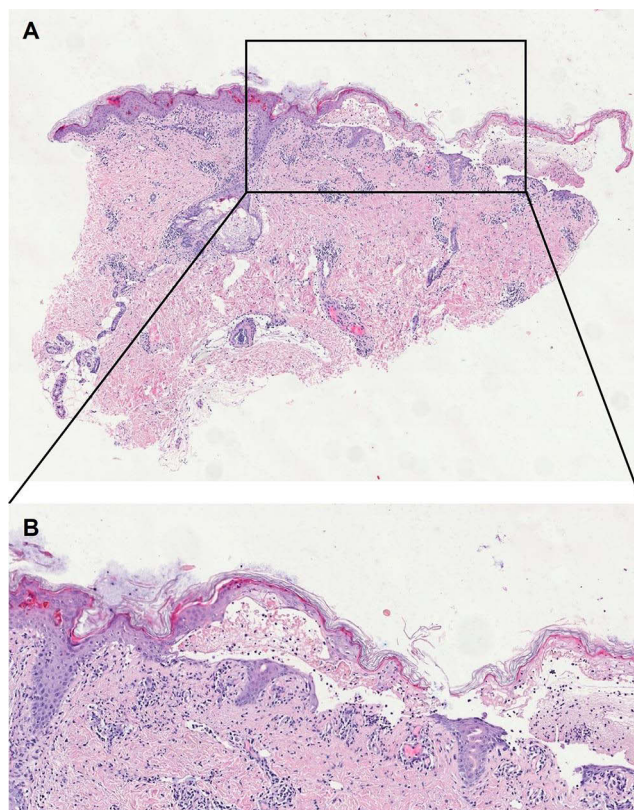
Further clinical examinations using sonography for the abdomen and echocardiography for the heart revealed no pathological findings.

## Dermatologic Consultation

A dermatologic consultation was performed for further classification of the skin reaction and its underlying cause. As a result, EM or a multi-sited fixed bullous drug exanthema due to ibuprofen was assumed based on the characteristics of the skin/mucosal reactions and medical history. Subsequently, a biopsy was performed. The histopathological examination revealed an orthokeratosis. In the border area of the biopsy, complete necrosis of the epidermis was observed accompanied by subepidermal cleft formation. Neutrophil granulocytes dominated within the resulting cleft. Moreover, isolated basal lymphocytes and focal vacuolar generation were observed next to the cleft. The corium showed an interstitial and perivascular infiltrate composed of lymphocytes, neutrophil granulocytes and single eosinophil granulocytes (see Figure 2). These findings were consistent with a fixed bullous drug exanthema, but EM could not be definitively excluded.

## Therapy

Ibuprofen was discontinued and the patient received paracetamol (600 mg) and/or metamizole (600 mg) as short infusions. In addition, metamizole was administered as continuous infusion (2300 mg; 2 mL/h) over five days. Due to the significant mucositis and swelling of the lips, the patient was unable to eat and drink properly. Consequently, parenteral nutrition and intravenous rehydration were initiated. The patient received prednisolone (80 mg per day) twice and immunoglobulins (2 g/kg) once. For treatment of the mucositis, a mucositis solution including lidocaine hydrochloride, benzydamine hydrochloride and dexpanthenol was used. Genital lesions were treated with octenidine and sitz baths with chamomile. The acute hemorrhagic conjunctivitis was treated with azithromycin (15 mg/g; 1 drop twice daily) and hyaluronic (1 mg/mL; 1 drop thrice daily) eye



**Figure 2** Histology of skin biopsy. **(A)** Overview of the skin biopsy. **(B)** Enlarged picture of the skin biopsy shows orthokeratosis with epidermal necrosis at the biopsy margin, subepidermal clefting filled with neutrophils, and adjacent basal vacuolar changes. The dermis contains interstitial and perivascular infiltrates of lymphocytes, neutrophils and rare eosinophils.

drops for three days. After another ophthalmological consultation, the medication was adjusted to ofloxacin (3 mg/mL; 1 drop twice daily) and hydrocortisone (3.35 mg/mL; 1 drop thrice daily) eye drops. In addition, antibiotic therapy with ampicillin and sulbactam (2+1) was started and switched to piperacillin and tazobactam (8+1) after one day, as the inflammation parameters increased. For treatment of *M. pneumoniae*, administration of clarithromycin (500 mg twice daily) was started and switched to doxycycline (75 mg once daily) after five days. Acyclovir (180 mg thrice daily) was initiated for the treatment of HSV and changed to valacyclovir (500 mg twice daily) after discharge from the hospital. In addition, epinephrine (4 mg/mL) was inhaled twice. [Table 3](#) provides details on the medications administered during hospitalization, including their dosages, frequency and duration of use.

After two weeks, the patient was discharged from the hospital. He was advised to avoid ibuprofen in the future and to use paracetamol instead. Moreover, the patch test in loco, as described earlier, with ibuprofen was recommended. In the meantime, the patient has fully recovered.

## Discussion

Several case reports describe a causal relation between the administration of ibuprofen and the occurrence of SJS in pediatric patients.<sup>3–5</sup> In the presented case, the patient was admitted to hospital with suspected SJS possibly related to the administration of ibuprofen. Ultimately, the suspected diagnosis of SJS was not confirmed in the hospital. Several blistering skin reactions can be classified: EM, SJS, toxic epidermal necrolysis (TEN) and generalized bullous fixed drug exanthema are accompanied by severe clinical implications for the patient.<sup>6,7</sup> Criteria such as skin detachment, target lesions (typical versus atypical), raised lesions and distribution are used to categorize these skin reactions (see [Table 4](#)).<sup>6</sup> However, in some cases, the exact classification still remains challenging. These skin reactions can be induced by several

**Table 3** Overview of Medications Administered During Hospitalization

Parameter	Dosage	Frequency	Duration
<b>Pain</b>			
Paracetamol i.v.	600 mg	2 x daily	Day 2
Metamizole i.v. (short infusion)	600 mg	2 x daily	Day 3
Metamizole i.v.	2 mL/h (2300 mg)	Continuous infusion	Day 3 - 7
<b>Nutrition</b>			
Parenteral nutrition i.v.	-	Continuous infusion	Day 3 - 14
Pediatric electrolyte solution i.v.	-	Continuous infusion	Day 1 - 14
<b>Skin reactions/mucosal lesions</b>			
Prednisolone i.v.	80 mg	1 x daily	Day 4, day 6
Immunoglobulins i.v.	70 g (2 g/kg)	Once	Day 7
Mucositis solution	15 mL	4 x daily	Day 2 - 14
Octenidine	-	3 x daily	Day 5 - 14
Sitz bath	-	1 x daily	Day 13 - 14
<b>Eyes</b>			
Azithromycin	1 drop (15 mg/g)	2 x daily	Day 4 - 7
Hyaluronic acid	1 drop (1 mg/mL)	3 x daily	Day 4 - 7
Ofloxacin	1 drop (3 mg/mL)	2 x daily	Day 7 - 14
Hydrocortisone	1 drop (3.35 mg/mL)	3 x daily	Day 8 - 14
<b>Infections</b>			
Ampicillin and sulbactam (2+1) i.v.	666.7 mg/333.3 mg	2 x daily	Day 1 - 2
Piperacillin and tazobactam (8+1) i.v.	3900 mg/487.5 mg	2 x daily	Day 2 - 4
Clarithromycin i.v.	500 mg	2 x daily	Day 2 - 6
Doxycycline i.v.	75 mg	1 x daily	Day 8 - 13
Acyclovir i.v.	180 mg	3 x daily	Day 9 - 14
Epinephrine inhalative	1 mL (4 mg/mL)	2 x daily	Day 4

**Abbreviations:** i.v., intravenous.

triggers including drugs as well as infections (Table 4).<sup>6</sup> Consequently, the determination of the trigger is crucial to choose an appropriate therapy regimen for the patient.

In children, 60 – 90% of SJS and TEN are caused by the administration of drugs.<sup>9</sup> Techasatian et al showed that antiepileptic drugs represent the most common cause (60%) for SJS and TEN in children, followed by antibiotics such as erythromycin and trimethoprim-sulfamethoxazole (26.6%) and other drugs (13.3%) including nonsteroidal anti-inflammatory drugs like ibuprofen.<sup>10</sup> However, no correlation between ibuprofen doses and occurrence/severity of skin lesions has been found in the literature. The latent period analyzed by Techasatian et al between drug administration and diagnosis ranged between 1 and 31 days, with a mean of 10.7 days.<sup>10</sup> Antiepileptic drugs showed the longest latency period compared to other drugs (median difference 11 days).<sup>10</sup>

**Table 4** Classification of Several Skin Reactions (Modified From<sup>6</sup>)

Criterion	EM	SJS	SJS/TEN overlap
Skin detachment (affected BSA)	<10%	<10%	10 – 30%
Target lesions	Typical and/or atypical	Atypical	Atypical
Raised lesions	Yes	No	No
Distribution	Predominantly extremities, in children frequently trunk	Predominantly trunk	Predominantly trunk
Main trigger	Infections <sup>8</sup>	Drugs <sup>9</sup>	Drugs <sup>9</sup>

**Box 1** summarizes the results of an analysis conducted in the EudraVigilance database to identify potential cases of Ibuprofen-associated SJS in the pediatric population.

Another skin reaction caused by drugs is the generalized bullous fixed drug exanthema, which can be clinically differentiated from SJS and TEN.<sup>11</sup> It is characterised by the presence of large areas of intact skin between the individual blisters and a better general condition of the patient than in SJS and TEN.<sup>11</sup> Recurrent episodes can lead to an increased severity of the symptoms.<sup>11</sup> In case of a drug-induced skin reaction, the medication has to be stopped immediately.<sup>6</sup>

In contrast, EM is mainly caused by infections (90%), especially by HSV and *M. pneumoniae*.<sup>8</sup> EM, related to drugs, is only reported for less than 10% of the cases.<sup>8</sup> If the skin reaction is caused by an infection, an appropriate medication should be started urgently.<sup>6</sup>

Moreover, the identification of *M. pneumoniae* should prompt consideration of a MIRM.<sup>12</sup> In addition to pneumonia, extrapulmonary manifestations are observed in approximately 25% of *M. pneumoniae* infections, with cutaneous involvement representing one of the most common complications.<sup>13</sup> MIRM must be distinguished clinically and histopathologically from other blistering skin reactions and predominantly affects children (mean age: 11.9 years) with approximately two-thirds of cases in male patients.<sup>14</sup> A case report in the literature describes a 9-year-old boy diagnosed with MIRM and a concurrent *H. simplex* infection.<sup>12</sup> In this instance, the viral infection was interpreted as secondary, likely originating from the mucosal lesions.<sup>12</sup> The similarities observed between this report and our case, combined with the predominance of MIRM among male children, underscore its relevance as a potential differential diagnosis.

In the presented case, the coexistence of several potential triggers made it very difficult to classify the skin reaction and its underlying cause.

After the positive laboratory tests with detection of HSV and *M. pneumoniae*, an infection-triggered skin reaction such as EM was suspected, as this association has been described in other children.<sup>15,16</sup> Moreover, the possibility of MIRM might be considered in this patient.<sup>12</sup> However, in previous episodes HSV and *M. pneumoniae* were not detectable. The serology findings regarding HSV were consistent with a primary infection.

The findings from the biopsy indicate a generalized fixed bullous drug reaction supporting the initial suspicion of a correlation with administration of ibuprofen. This diagnosis would fit with the increasing severity of symptoms with each subsequent episode, as described in the literature.<sup>11</sup> In previous episodes, the symptoms were less pronounced compared to the current episode. Moreover, some of the earlier episodes were treated in an outpatient setting, whereas this episode required a stay of two weeks in the pediatric hospital. However, an exact differentiation of the generalized

#### **Box 1** Spontaneous reports of SJS associated with ibuprofen in the EU

An assessment of the EudraVigilance database was conducted. In this analysis, the number of reported pediatric SJS cases potentially associated with ibuprofen was determined. In the pediatric group (0 to ≤17 years), a total of 159 cases were found to have a possible or confirmed association with the administration of ibuprofen in the time period of 2014 – 2024 (adrreports.eu; 5 February 2025).

fixed bullous drug exanthema from an EM was not possible based on the results of the biopsy. This should be clarified with an allergological work-up.

When a causal connection between a skin reaction and drug administration cannot be excluded, it is important to report the adverse event in accordance with the national regulations. This is especially important for children, as they may be more vulnerable to adverse reactions.<sup>17</sup> These reports contribute to more knowledge and awareness in the field of pediatric drug safety. The presented case was reported to the Drug Commission of the German Medical Association.

## Conclusion

This report demonstrates the difficulty of the classification and determination of triggers in skin reactions. However, classification of the skin reaction and its underlying cause plays a decisive role in the therapy and prevention. Moreover, this case report aims to raise awareness of the possible relationship between drug administration and severe skin reactions, especially in pediatric patients. In the presented case, the underlying cause for the clinical symptoms remained uncertain; however, a relationship between the administration of ibuprofen and the occurrence of this skin reaction is possible. Finally, an extensive therapeutic regimen over two weeks of hospitalization resulted in complete recovery of the patient.

## Institutional Approval

No institutional approval was required for publication of this case.

## Patient Consent for Publication

Written consent from the parents for the publication of this case report has been obtained.

## Acknowledgments

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## Disclosure

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