Clinical presentation and management of children with suspected serum sickness–like reaction

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Clinical Implications

Serum sickness–like reaction (SSLR) is a rare diagnosis that occurs after drug exposure. SSLR is a challenging diagnosis resulting in multiple health care visits, hospitalizations, and varied treatment. Our findings support the need for the development of SSLR clinical diagnostic criteria and treatment guidance.

Serum sickness–like reaction (SSLR) is typically associated with fever, rash, and joint symptoms after exposure to a drug. The pathophysiology is not well understood and is thought to arise from drug metabolites (haptens) binding to plasma proteins that induce an abnormal immunologic response.[1] Several drugs including antibiotics have been associated with SSLR. Historically cefaclor was commonly implicated; however, more recently additional antibiotics including penicillin have been described.[1,2]

Symptoms present 5 to 21 days after drug exposure and vary in presentation including rash that appears as urticaria, morbilliform, annular plaques with central clearing, and erythema multiforme–like lesions,[3-5] as well as bilateral joint involvement commonly in the hands and feet.[6,7] Currently, there are no standardized criteria to diagnose SSLR and no guidelines for treatment, leading to delay in diagnosis and variation in management.

Once diagnosed, the lack of standardized treatment results in management variability. Most treatment strategies include antihistamines, anti-inflammatory agents, and corticosteroids,[6] though symptoms are typically self-resolving. The degree to which management of SSLR varies within the emergency department (ED) and inpatient settings is currently unknown.

In this study, we aimed to better understand SSLR diagnostic and treatment approaches in the pediatric population. We reviewed SSLR cases at 2 large tertiary-care pediatric centers. We describe the implicated medication triggers, clinical manifestations, and management of pediatric SSLR both in the hospital and ED to help guide practitioners in considering SSLR in their differential.

We performed a retrospective cohort study of children ≤18 years of age who presented to the ED or were admitted at Children's Mercy Kansas City (CMKC) in Kansas City, Mo, or Riley Children's Hospital at Indiana University Health (IUH) in Indianapolis, Ind, between January 1, 2015, and December 31, 2021. The study protocol and materials were approved by the CMKC institutional review board and IUH human research protection program.

Inclusion criteria included an SSLR diagnosis code, defined by International Classification of Diseases, 9th/10th Revision (ICD-9/10) (999.59, T80.69XA), or SNOMED (1782626019, 3293325014) codes. Additional patients were identified through each hospital's pharmacovigilance program that review all adverse drug reactions in the medical record for further documentation and clarification.[8] Medical records of identified patients were reviewed to confirm that SSLR was documented as the discharge diagnosis by the treating clinician. Patients without an associated implicated drug or those evaluated outside of the ED or inpatient setting were excluded from this study. We additionally excluded biologics, vaccines, and chemotherapeutic agents as these are more commonly associated with true serum sickness rather than SSLR. All cases without documented arthralgia were subsequently excluded as joint involvement is considered characteristic along with rash and fever.

A total of 171 children were included in this study with a mean age of 4.2 years at the time of diagnosis. Most patients (99%) were previously healthy without any known medical history. Demographic characteristics are summarized in Table I.

Antibiotics were the most commonly implicated drug class associated with SSLR, with a majority being amoxicillin and amoxicillin/clavulanate (n = 132; 77%). Twelve patients received a subsequent antibiotic in a different antibiotic class before the SSLR diagnosis. Indications for antibiotics were most commonly acute otitis media (n = 102; 60%). Of note, several patients received antibiotics for viral symptoms or without a specific infectious indication.

Fifty-nine percent of patients presented with symptoms while actively taking the suspected drug. Most common symptoms included rash (n = 169; 99%) and documented fever of ≥38°C (n = 67; 39%). Rashes were primarily described as erythematous and maculopapular, though further characterization was difficult due to limited clinician documentation. Joint symptoms presented as edema (n = 152; 89%), pain (n = 106; 62%), stiffness (n = 8; 5%), and erythema (n = 27; 16%). Most patients (n = 133; 78%) had ≥4 joints involved. Facial edema (n = 53; 31%) and gastrointestinal symptoms (n = 49; 29%) were also documented in several patients.

Sixty-eight percent of patients had labs collected. Overall, labs were relatively unremarkable with a median white blood count value of 13.8×10^3 (interquartile range [IQR]: 11.55-17.21), median erythrocyte sedimentation rate of 15 mm/h (IQR: 7.25-26.75 mm/h), and a median C-reactive protein of 3.4 mg/dL (IQR: 0.85-5.75 mg/dL). Thirty-five percent of patients with available testing had a white blood count above the upper limit of normal, 57% with an erythrocyte sedimentation rate >13 mm/h, and 71% with a C-reactive protein >1 mg/dL. Only 6.4% of patients with labs had a complement level obtained, and all complement levels were within normal range.

Treatment approaches for SSLR varied (Table II). Most children were treated with antihistamines, acetaminophen, and nonsteroidal anti-inflammatory drugs, with 87 patients receiving >1 antihistamine. Over 50% of patients were managed with corticosteroids.

SSLR was rarely included in the initial differential (n = 49, 29%) and often required subsequent visits (mean = 2.04 visits)

TABLE I. Demographics of patients with SSLR, implicated drugs associated with SSLR diagnosis, and SSLR symptoms (N = 171)

Characteristics	Value
Demographic characteristics, n (%)	
Sex, male	97 (57)
Age at diagnosis (y), mean ± SD	4.2 ± 3.9
Ethnic origin	
White	141 (82.5)
African American	9 (5.3)
Hispanic	4 (2.3)
Asian	1 (0.6)
Other	4 (2.3)
Multiracial	4 (2.3)
Unknown	8 (4.7)
Implicated drug, n (%)	
Amoxicillin ± clavulanate	132 (77)
Cefdinir	15 (9)
Trimethoprim/sulfamethoxazole	2 (1)
Cephalexin	3 (2)
2+ antibiotics	12 (7)
Other	7 (4)
Indication for implicated drug, n (%)	
Acute otitis media	102 (60)
Streptococcus pharyngitis	23 (13)
Pneumonia	7 (4)
Dental	4 (2)
Skin infections	3 (2)
Acne	4 (2)
Urinary tract infection	2 (1)
Viral illness	5 (3)
2+ diagnoses	9 (5)
Other	7 (4)
Unknown	5 (3)
Symptoms, n (%)	
Rash	169 (99)
Joint symptoms	
Joint edema	152 (89)
Joint pain	106 (62)
Joint stiffness	8 (5)
Joint erythema	27 (16)
Fever	67 (39)
Mobility limited	64 (37)
Facial edema	53 (31)
Gastrointestinal symptoms	49 (29)
Malaise	10 (6)
Myalgias	11 (6)
Conjunctivitis	6 (4)
Mucosal involvement	7 (4)
Headache	6 (4)
Lymphadenopathy	4 (2)

SD, Standard deviation; *SSLR*, serum sickness–like reaction.

TABLE II. Treatment used in patients with SSLR

Treatment	Total cohort (N = 171), n (%)	ED (n = 91), n (%)	Inpatient (n = 80), n (%)
Any antihistamine	158 (92)	84 (92)	74 (93)
Acetaminophen	105 (61)	44 (48)	61 (76)
NSAIDs	139 (81)	70 (77)	69 (86)
Opioids	6 (4)	0 (0)	6 (8)
Steroids	91 (53)	42 (46)	49 (61)
Epinephrine	8 (5)	1 (1)	7 (9)
Acid reducer	36 (21)	18 (20)	18 (23)

NSAID, Nonsteroidal anti-inflammatory drug; *SSLR*, serum sickness–like reaction.

for the diagnosis. Although SSLR can typically be managed outpatient, 47% of our cohort were admitted with a mean duration of 1.20 days (standard deviation: ±1.25, range: 0-5 days). Once admitted, patients were more likely to be treated with corticosteroids (61% vs 46%, $P = .07$), have labs drawn (89% vs 50%, $P < .001$), and involve a consulting service (55% vs 21%, $P < .001$) compared with those who were managed in the ED setting alone. Multivariate analysis of symptomatology (adjusted for age, sex, number of prior visits [discretized 1 vs 1+], and hospital system) demonstrated that fever (odds ratio: 4.44 [95% confidence interval: 2.21-8.91], $P < .001$), limited mobility (1.97 [0.99-3.92], $P = .05$), facial edema (2.67 [1.29-5.49], $P = .01$], and joint pain (1.94 [0.94-4.03], $P = .08$) were associated with increased odds of hospitalization.

To our knowledge, this is the largest study describing pediatric SSLR. We found that antibiotics are commonly implicated, inflammatory labs may be mildly elevated but nonspecific, and treatment varies including hospitalization of the patient.

There is likely an opportunity to create SSLR criteria with the utilization of specific clinical findings such as rash, multiple joint involvement, fever, with possible facial edema and/or gastrointestinal symptoms, in combination with normal to modestly elevated laboratory values to aid in the diagnosis. As subspecialists are often unavailable in outpatient, ED, and community settings, improved diagnostic criteria would assist the clinician who may be relatively unfamiliar with SSLR. The development of clinical diagnostic criteria may also help reduce health care visits and optimize treatment management.

The decision to admit patients with SSLR may be multifactorial including parental concern for an immobile child or continued workup such as a septic joint or adverse drug reaction with facial edema. *In vitro* testing such as a lymphocyte toxicity assay may serve as a beneficial diagnostic indicator for SSLR,[9] though this is not a test frequently used in clinical practice to aid in the diagnosis. Addition evaluation of integrating diagnostic tests such as lymphocyte toxicity assays is needed to understand the utility in the clinical setting, particularly in outpatient and ED settings.

This study did not evaluate the outcomes of SSLR treatment. Further evaluation for treatment selection could be helpful to prevent prolonged corticosteroid overuse. Prospective studies to better understand corticosteroid use including formulation, dosing, duration, and alternative steroid-sparing therapies such as antihistamines and/or anti-inflammatory agents are needed.

The main limitation to this study is its retrospective design. Due to lack of clinical criteria, the selection of included cases was dependent on the presence of an SSLR documented diagnosis likely underestimating the incidence as well as the potential for misdiagnosis. Dermatology consultation occurred infrequently, including for cases that were atypical (eg, cases with conjunctivitis or mucositis), suggesting that alternative diagnoses could have been possible.

We hope that this study will encourage clinicians to consider SSLR on the differential with patients who present with symptoms including rash, joint involvement, fever, and facial edema with recent antibiotic exposure. Future work should evaluate optimal diagnostic criteria and treatment options to enhance patient care.

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